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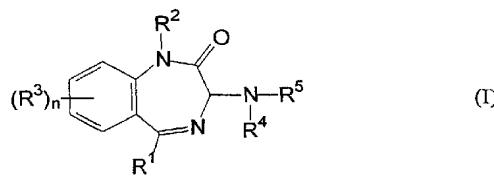
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(54) Title: BENZODIAZEPINE DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM



(57) Abstract: Benzodiazepine derivative of formula (I), and pharmaceutically acceptable salts thereof, are found to be active against RSV. Formula (I) Wherein: - R¹ represents C₁₋₆ alkyl, aryl or heteroaryl; - R² represents hydrogen or C₁₋₆ alkyl; - each R³ is the same or different and represents halogen, hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, amino, mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, nitro, cyano, -CO₂R¹, -CONR¹R², -NH-CO-R¹, -S(O)R¹, -S(O)₂R¹, -NH-S(O)₂R¹, -S(O)NR¹R² or -S(O)₂NR¹R² wherein each R¹ and R² is the same or different and represents hydrogen or C₁₋₆ alkyl; - n is from 0 to 3; R⁴ represents hydrogen or C₁₋₆ alkyl; - R⁵ represents C₁₋₆ alkyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C₁₋₆ alkyl)-, heteroaryl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆ alkyl)-, heterocyclyl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆ alkyl)-, heterocyclyl-(C₁₋₆ alkyl)-, aryl-(C₁₋₆ hydroxyalkyl)-, heteroaryl-(C₁₋₆ hydroxyalkyl)-, carbocyclyl-(C₁₋₆ hydroxyalkyl)-, heterocyclyl-(C₁₋₆ hydroxyalkyl)-, aryl-(C₁₋₆ alkyl)-O-, heteroaryl-(C₁₋₆ alkyl)-O-, carbocyclyl-(C₁₋₆ alkyl)-O-, heterocyclyl-(C₁₋₆ alkyl)-O- or -NR¹R² wherein each R¹ and R² is the same or different and represents hydrogen, C₁₋₆ alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C₁₋₆ alkyl)-, heteroaryl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆ alkyl)- or heterocyclyl-(C₁₋₆ alkyl)-.

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BENZODIAPINE DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

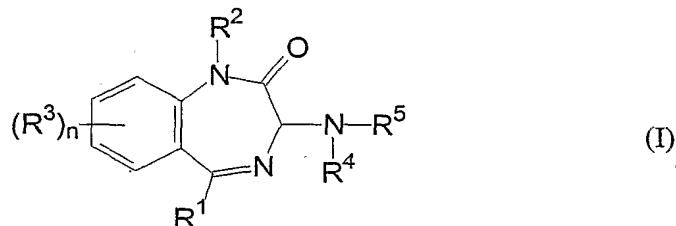
The present invention relates to a series of benzodiazepine derivatives
5 which are active against Respiratory Syncytial Virus (RSV).

RSV is a major cause of respiratory illness in patients of all ages. In adults, it tends to cause mild cold symptoms. In school-aged children, it can cause a cold and bronchial cough. In infants and toddlers it can cause bronchiolitis (inflammation of the smaller airways of the lungs) or pneumonia. It has also been 10 found to be a frequent cause of middle ear infections (otitis media) in pre-school children. RSV infection in the first year of life has been implicated in the development of asthma during childhood.

Current anti-RSV therapy involves the use of a monoclonal antibody to RSV, called palivizumab. Such use of palivizumab is a prophylactic, rather than 15 therapeutic, treatment of RSV. However, although this antibody is often effective, it is expensive. Indeed, its expense means that it is unavailable for many people in need of anti-RSV therapy. There is therefore an urgent need for effective alternatives to existing anti-RSV therapy.

It has now surprisingly been found that the particular benzodiazepine 20 derivatives of the general formula (I) set out below are active against RSV.

Accordingly, the present invention provides, in a first embodiment, the use of a benzodiazepine derivative of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in treating or preventing an RSV infection



25

wherein:

R¹ represents C₁₋₆ alkyl, aryl or heteroaryl;

- R^2 represents hydrogen or C_{1-6} alkyl;
- each R^3 is the same or different and represents halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, amino, mono(C_{1-6} alkyl)amino, di(C_{1-6} alkyl)amino, nitro, cyano, $-CO_2R'$, $-CONR'R''$, $-NH-CO-R'$, $-S(O)R'$, $-S(O)_2R'$, $-NH-S(O)_2R'$, $-S(O)NR'R''$ or $-S(O)_2NR'R''$, wherein each R' and R'' is the same or different and represents hydrogen or C_{1-6} alkyl;
- 5 - n is from 0 to 3;
- R^4 represents hydrogen or C_{1-6} alkyl;
- R^5 represents C_{1-6} alkyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6} alkyl)-, carbocyclyl-(C_{1-6} alkyl)-, heterocyclyl-(C_{1-6} alkyl)-aryl-C(O)-C(O)-, heteroaryl-C(O)-C(O)-, carbocyclyl-C(O)-C(O)-, heterocyclyl-C(O)-C(O)- or $-XR^6$;
- X represents $-CO-$, $-S(O)-$ or $-S(O)_2-$; and
- R^6 represents C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, aryl, heteroaryl, 10 carbocyclyl, heterocyclyl, aryl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6} alkyl)-, carbocyclyl-(C_{1-6} alkyl)-, heterocyclyl-(C_{1-6} alkyl)-, aryl-(C_{1-6} hydroxyalkyl)-, heteroaryl-(C_{1-6} hydroxyalkyl)-, carbocyclyl-(C_{1-6} hydroxyalkyl)-, heterocyclyl-(C_{1-6} hydroxyalkyl)-, aryl-(C_{1-6} alkyl)-O-, heteroaryl-(C_{1-6} alkyl)-O-, carbocyclyl-(C_{1-6} alkyl)-O-, heterocyclyl-(C_{1-6} alkyl)-O- or $-NR'R''$ wherein each R' and R'' is the same or 15 different and represents hydrogen, C_{1-6} alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6} alkyl)-, carbocyclyl-(C_{1-6} alkyl)- or heterocyclyl-(C_{1-6} alkyl)-. Typically, R' and R'' are not both hydrogen.
- 20

Preferably, in the formula (I),

- each R^3 is the same or different and represents halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, amino, mono(C_{1-6} alkyl)amino, di(C_{1-6} alkyl)amino, nitro, cyano, $-CO_2R'$, $-CONR'R''$, $-NH-CO-R'$, $-S(O)R'$, $-S(O)_2R'$, $-NH-S(O)_2R'$ or $-S(O)NR'R''$, wherein each R' and R'' is the same or different and represents hydrogen or C_{1-6} alkyl;
- R^5 represents C_{1-6} alkyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6} alkyl)-, carbocyclyl-(C_{1-6} alkyl)-, heterocyclyl-(C_{1-6} alkyl)- or $-XR^6$;
- X represents $-CO-$, $-S(O)-$ or $-S(O)_2-$; and

- R^6 represents C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6} alkyl)-, carbocyclyl-(C_{1-6} alkyl)-, heterocyclyl-(C_{1-6} alkyl)- or $-NR' R''$ wherein each R' and R'' is the same or different and represents hydrogen, C_{1-6} alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C_{1-6} alkyl)- or heteroaryl-(C_{1-6} alkyl)-. Typically, R' and R'' are not both hydrogen.

As used herein, a C_{1-6} alkyl group or moiety is a linear or branched alkyl group or moiety containing from 1 to 6 carbon atoms, such as a C_{1-4} alkyl group or moiety. Examples of C_{1-4} alkyl groups and moieties include methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl and *t*-butyl. For the avoidance of doubt, where two alkyl moieties are present in a group, the alkyl moieties may be the same or different.

As used herein, a hydroxyalkyl group is typically a said alkyl group that is substituted by one or more hydroxy groups. Typically, it is substituted by one, two or three hydroxy groups. Preferably, it is substituted by a single hydroxy group.

15 Preferred hydroxyalkyl groups are (monohydroxy)ethyl groups.

As used herein, an acyl group is a C_{2-7} acyl group, for example a group $-CO-R$, wherein R is a said C_{1-6} alkyl group.

As used herein, an aryl group is typically a C_{6-10} aryl group such as phenyl or naphthyl. Phenyl is preferred. An aryl group may be unsubstituted or substituted at any position. Typically, it carries 0, 1, 2 or 3 substituents.

20 Suitable substituents on an aryl group include halogen, C_{1-6} alkyl, C_{2-7} acyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, nitro, cyano, carbamoyl, mono(C_{1-6} alkyl)carbamoyl, di(C_{1-6} alkyl)carbamoyl, amino, mono(C_{1-6} alkyl)amino, di(C_{1-6} alkyl)amino, $-CO_2R'$, $-CONR' R''$, $-S(O)R'$, $-S(O)_2R'$, $-S(O)NR' R''$, $-S(O)_2NR' R''$, $-NH-S(O)_2R'$ or $-NH-CO-R'$, wherein each R' and R'' is the same or different and represents hydrogen or C_{1-6} alkyl. Examples of suitable substituents on an aryl group include halogen, C_{1-6} alkyl, C_{2-7} acyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, nitro, cyano, carbamoyl, mono(C_{1-6} alkyl)carbamoyl, di(C_{1-6} alkyl)carbamoyl, amino, mono(C_{1-6} alkyl)amino, di(C_{1-6} alkyl)amino, $-CO_2R'$, $-CONR' R''$, $-S(O)R'$, $-S(O)_2R'$, $-S(O)NR' R''$, $-NH-S(O)_2R'$ or $-NH-CO-R'$, wherein each R' and R'' is the same or different and represents hydrogen or C_{1-6} alkyl.

Preferred substituents on an aryl group include halogen, C₁₋₆ alkyl, C₂₋₇ acyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, amino, mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, nitro, cyano, -CO₂R', -S(O)R', -S(O)₂R' and -S(O)₂NR'R'', wherein each R' and R'' is the same or different and represents

5 hydrogen or C₁₋₄ alkyl. Examples of preferred substituents on an aryl group include halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, nitro and cyano.

Particularly preferred substituents include fluorine, chlorine, bromine, iodine, C₁₋₄ alkyl, C₂₋₄ acyl, hydroxy, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, amino, mono(C₁₋₄ alkyl)amino, di(C₁₋₄ alkyl)amino, nitro, -CO₂R', -S(O)₂R' and -S(O)₂NH₂, wherein R' represents C₁₋₂ alkyl. Examples of particularly preferred substituents include fluorine, chlorine, bromine, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl and nitro.

As used herein, references to an aryl group include fused ring systems in which an aryl group is fused to a monocyclic carbocyclyl, heterocyclyl or heteroaryl group or to a fused group which is a monocyclic carbocyclyl, heterocyclyl or heteroaryl group which is fused to a phenyl ring. Typically, said fused ring systems are systems in which an aryl group is fused to a monocyclic carbocyclyl, heterocyclyl or heteroaryl group. Preferred such ring systems are those wherein an aryl group is fused to a fused group which is a monocyclic heterocyclyl or heteroaryl group or to a monocyclic carbocyclic group fused to a phenyl ring, in particular those wherein an aryl group is fused to a heterocyclyl or heteroaryl group. Examples of such fused ring systems are groups in which a phenyl ring is fused to a thienyl group or to a tetrahydrofuranyl group to form a benzothienyl or dihydrobenzofuranyl group. Further examples of such fused rings are groups in which a phenyl ring is fused to a dioxanyl group, a pyrrolyl group or a 2,3-dihydroinden-1-one group to form a benzodioxinyl, indolyl or a 9H-fluoren-9-one group.

As used herein, a carbocyclyl group is a non-aromatic saturated or unsaturated monocyclic hydrocarbon ring, typically having from 3 to 6 carbon atoms. Preferably it is a saturated hydrocarbon ring (i.e. a cycloalkyl group) having from 3 to 6 carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. It is preferably cyclopentyl or cyclohexyl. A cycloalkyl group may be

unsubstituted or substituted at any position. Typically, it carries 0, 1, 2 or 3 substituents.

Suitable substituents on a carbocyclyl group include halogen, C₁₋₆ alkyl, C₂₋₇ acyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, 5 nitro, cyano, carbamoyl, mono(C₁₋₆ alkyl)carbamoyl, di(C₁₋₆ alkyl)carbamoyl, amino, mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, oxo, -CO₂R', -CONR'R'', -S(O)R', -S(O)₂R', -S(O)NR'R'', -S(O)₂NR'R'', -NH-S(O)₂R' or -NH-CO-R', wherein each R' and R'' is the same or different and represents hydrogen or C₁₋₆ alkyl. Examples of suitable substituents on a carbocyclyl group include halogen, C₁₋₆ alkyl, C₂₋₇ acyl, 10 hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, nitro, cyano, carbamoyl, mono(C₁₋₆ alkyl)carbamoyl, di(C₁₋₆ alkyl)carbamoyl, amino, mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, -CO₂R', -CONR'R'', -S(O)R', -S(O)₂R', -S(O)NR'R'', -NH-S(O)₂R' or -NH-CO-R', wherein each R' and R'' is the same or different and represents hydrogen or C₁₋₆ alkyl.

15 Preferred substituents on an carbocyclyl group include halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, nitro, cyano and oxo. Examples of preferred substituents on an carbocyclyl group include halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, mono(C₁₋₆ alkyl)amino, di(C₁₋₆ 20 alkyl)amino, nitro and cyano. Particularly preferred substituents include fluorine, chlorine, bromine, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, nitro and oxo. Examples of particularly preferred substituents include fluorine, chlorine, bromine, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl and nitro. Further examples of particularly preferred substituents include fluorine, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl and nitro.

25 As used herein, a heterocyclyl group is a non-aromatic saturated or unsaturated carbocyclic ring typically having from 5 to 10 carbon atoms, in which one or more, for example 1, 2 or 3, of the carbon atoms is replaced by a heteroatom selected from N, O and S. Saturated heterocyclyl groups are preferred. Examples include tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl, imidazolidinyl, 30 pyrazolidinyl, dioxolanyl, thiazolidinyl, tetrahydropyranyl, piperidinyl, dioxanyl, piperazinyl, morpholinyl, thiomorpholinyl and thioxanyl. Further examples include

dithiolanyl, oxazolidinyl, tetrahydrothiopyranyl and dithianyl. Piperazinyl, piperidinyl and morpholinyl are preferred.

As used herein, references to a heterocyclyl group include fused ring systems in which a heterocyclyl group is fused to a phenyl group. Preferred such 5 fused ring systems are those wherein a 5- to 6-membered heterocyclyl group is fused to a phenyl group. An example of such a fused ring system is a group wherein a 1H-imidazol-2(3H)-onyl group or a imidazolidin-2-onyl group is fused to a phenyl ring to form a 1H-benzo[d]imidazol-2(3H)-onyl group. Most preferably, however, a heterocyclyl group is monocyclic.

10 A heterocyclic group may be unsubstituted or substituted at any position. Typically, it carries 0, 1 or 2 substituents.

Suitable substituents on a heterocyclyl group include halogen, C₁₋₆ alkyl, C₂₋₇ acyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, nitro, cyano, carbamoyl, mono(C₁₋₆ alkyl)carbamoyl, di(C₁₋₆ alkyl)carbamoyl, amino, 15 mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, oxo, -CO₂R', -CONR'R'', -S(O)R', -S(O)₂R', -S(O)NR'R'', -S(O)₂NR'R'', -NH-S(O)₂R' or -NH-CO-R', wherein each R' and R'' is the same or different and represents hydrogen or C₁₋₆ alkyl. Examples of suitable substituents on a heterocyclyl group include halogen, C₁₋₆ alkyl, C₂₋₇ acyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, nitro, cyano, 20 carbamoyl, mono(C₁₋₆ alkyl)carbamoyl, di(C₁₋₆ alkyl)carbamoyl, amino, mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, -CO₂R', -CONR'R'', -S(O)R', -S(O)₂R', -S(O)NR'R'', -NH-S(O)₂R' or -NH-CO-R', wherein each R' and R'' is the same or different and represents hydrogen or C₁₋₆ alkyl.

Preferred substituents on a heterocyclyl group include halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, nitro, cyano and oxo. Examples of preferred substituents on a heterocyclyl group include halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, nitro and cyano. Particularly preferred substituents include fluorine, 25 chlorine, bromine, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, nitro and oxo. Examples of particularly preferred substituents include fluorine, chlorine, bromine, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl and nitro. Further examples of particularly preferred

substituents include fluorine, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl and nitro. Most preferably, a heterocyclyl group is unsubstituted or substituted by one or two C₁₋₂ alkyl groups.

As used herein, a halogen is typically chlorine, fluorine, bromine or iodine. It is preferably chlorine, fluorine or bromine. It is more preferably chlorine or fluorine.

As used herein, an alkoxy group is typically a said alkyl group attached to an oxygen atom. An alkylthio group is typically a said alkyl group attached to a thio group. A haloalkyl or haloalkoxy group is typically a said alkyl or 10 alkoxy group substituted by one or more said halogen atoms. Typically, it is substituted by 1, 2 or 3 said halogen atoms. Preferred haloalkyl and haloalkoxy groups include perhaloalkyl and perhaloalkoxy groups such as -CX₃ and -OCX₃ wherein X is a said halogen atom, for example chlorine or fluorine. Particularly preferred haloalkyl groups are -CF₃ and -CCl₃. Particularly preferred haloalkoxy groups are -OCF₃ and -OCCl₃.

As used herein, a heteroaryl group is typically a 5- to 10-membered aromatic ring, such as a 5- or 6-membered ring, containing at least one heteroatom, for example 1, 2 or 3 heteroatoms, selected from O, S and N. Examples include pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, furanyl, thienyl, pyrazolidinyl, pyrrolyl, 20 oxadiazolyl, isoxazolyl, thiadiazolyl, thiazolyl, imidazolyl and pyrazolyl groups. Further examples include oxazolyl and isothiazolyl. Preferred heteroaryl groups are pyridyl, thienyl, oxazolyl, isoxazolyl, furanyl and pyrazolyl. Examples of preferred heteroaryl groups are pyridyl, thienyl, isoxazolyl and furanyl. As used herein, references to a heteroaryl groups include fused ring systems in which a heteroaryl 25 group is fused to a phenyl group. Preferred such fused ring systems are those wherein a 5- to 6-membered heteroaryl group is fused to a phenyl group. Examples of such fused ring systems are benzofuranyl, benzothiophenyl, indolyl, benzimidazolyl, benzoxazolyl, quinolinyl, quinazolinyl and isoquinolinyl moieties. Most preferably, however, a heterocyclyl group is monocyclic.

30 A heteroaryl group may be unsubstituted or substituted at any position. Typically, it carries 0, 1, 2 or 3 substituents.

Suitable substituents on a heteroaryl group include halogen, C₁₋₆ alkyl, C₂₋₇

acyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, nitro, cyano, carbamoyl, mono(C₁₋₆ alkyl)carbamoyl, di(C₁₋₆ alkyl)carbamoyl, amino, mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, -CO₂R', -CONR'R'', -S(O)R', -S(O)₂R', -S(O)NR'R'', -S(O)₂NR'R'', -NH-S(O)₂R' or -NH-CO-R', wherein each R' and R'' is the same or different and represents hydrogen or C₁₋₆ alkyl. Examples of suitable substitutents on a heteroaryl group include halogen, C₁₋₆ alkyl, C₂₋₇ acyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, nitro, cyano, carbamoyl, mono(C₁₋₆ alkyl)carbamoyl, di(C₁₋₆ alkyl)carbamoyl, amino, mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, -CO₂R', -CONR'R'', -S(O)R', -S(O)₂R', -S(O)NR'R'', -NH-S(O)₂R' or -NH-CO-R', wherein each R' and R'' is the same or different and represents hydrogen or C₁₋₆ alkyl.

Preferred substituents on a heteroaryl group include halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, nitro and cyano. Particularly preferred substituents include fluorine, chlorine, bromine, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl and nitro. Further preferred substituents include fluorine, chlorine, bromine, C₁₋₂ alkyl, C₁₋₂ haloalkyl and di(C₁₋₂ alkyl)amino.

As used herein, references to a heteroaryl group include fused ring systems in which a heteroaryl group is fused to a monocyclic said aryl, carbocyclyl or heterocyclyl group, or to a further heteroaryl group. Preferred such ring systems are those wherein a heteroaryl group is fused to an aryl group, for example a phenyl group. An example of such a fused ring system is a group wherein a thieryl group is fused to a phenyl ring to form a benzothienyl group. A further example of such a fused ring system is a group wherein a furanyl group is fused to a phenyl ring to form a benzofuranyl group.

When R¹ is an aryl or heteroaryl group it is typically unsubstituted or substituted by one, two or three substituents selected from halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl or C₁₋₆ haloalkoxy. Preferably, it is unsubstituted or substituted by one or two substituents selected from fluorine, chlorine, bromine, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ haloalkyl or C₁₋₄ haloalkoxy. More preferably, it is unsubstituted or substituted by a single fluorine, chlorine, C₁₋₂ alkyl, C₁₋₂ alkoxy, C₁₋₂ alkylthio, C₁₋₂ haloalkyl or C₁₋₂ haloalkoxy.

substituent.

Typically, R¹ is C₁₋₆ alkyl or aryl. Preferably, R¹ is C₁₋₂ alkyl or aryl. More preferably, R¹ is C₁₋₂ alkyl or phenyl. More preferably, R¹ is phenyl.

Typically, R² is hydrogen or C₁₋₄ alkyl. Preferably, R² is hydrogen.

5 Typically, R³ is halogen, hydroxy, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, amino, mono(C₁₋₄ alkyl)amino or di(C₁₋₄ alkyl)amino. Preferably, R³ is fluorine, chlorine, bromine, C₁₋₂ alkyl, C₁₋₂ alkoxy, C₁₋₂ alkylthio, C₁₋₂ haloalkyl, C₁₋₂ haloalkoxy, amino, mono(C₁₋₂ alkyl)amino or di(C₁₋₂ alkyl)amino. More preferably, R³ is methyl, trifluoromethyl, fluorine, 10 chlorine or bromine. Most preferably, R³ is methyl or chlorine. An example of a most preferred group is when R³ is chlorine.

Typically, n is 0, 1 or 2. Preferably, n is 0 or 1.

Typically, R⁴ is hydrogen or C₁₋₄ alkyl. Preferably, R⁴ is hydrogen or C₁₋₂ alkyl. More preferably, R⁴ is hydrogen or methyl. Most preferably, R⁴ is 15 hydrogen

When R⁵ is a heterocyclyl group, it is typically attached via a carbon atom. Typically, R⁵ is C₁₋₆ alkyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C₁₋₄ alkyl)-, heteroaryl-(C₁₋₄ alkyl)-, carbocyclyl-(C₁₋₄ alkyl)-, heterocyclyl-(C₁₋₄ alkyl)-, aryl-C(O)-C(O)-, heteroaryl-C(O)-C(O)- or -XR⁶. Examples of typical R⁵ 20 groups are those wherein R⁵ is C₁₋₆ alkyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C₁₋₄ alkyl)-, heteroaryl-(C₁₋₄ alkyl)-, carbocyclyl-(C₁₋₄ alkyl)-, heterocyclyl-(C₁₋₄ alkyl)- or -XR⁶.

Preferably, R⁵ is C₁₋₄ alkyl, aryl, for example phenyl and dihydrobenzofuranyl, heteroaryl, for example thienyl, furanyl, isoxazolyl, pyridyl 25 and benzothienyl, carbocyclyl, for example cyclopentyl and cyclohexyl, heterocyclyl, for example piperidinyl, morpholinyl and piperazinyl, phenyl-(C₁₋₂ alkyl)-, for example benzyl, heteroaryl-(C₁₋₂ alkyl)-, phenyl-C(O)-C(O)-, heteroaryl-C(O)-C(O)- or -XR⁶. Examples of preferred R⁵ groups are those wherein R⁵ is C₁₋₄ alkyl, aryl, for example phenyl and dihydrobenzofuranyl, heteroaryl, for example 30 thienyl, furanyl, isoxazolyl, pyridyl and benzothienyl, carbocyclyl, for example cyclopentyl and cyclohexyl, heterocyclyl, for example piperidinyl, morpholinyl and piperazinyl, phenyl-(C₁₋₂ alkyl)-, for example benzyl, heteroaryl-(C₁₋₂ alkyl)- or -XR⁶.

More preferably, R^5 is C_{1-4} alkyl, phenyl, thienyl, furanyl, isoxazolyl, pyridyl, cyclopentyl, cyclohexyl, benzothienyl, dihydrobenzofuranyl, phenyl- CH_2 -, furanyl- CH_2 -, phenyl-C(O)-C(O)-, thienyl-C(O)-C(O)- or - XR^6 . Examples of more preferred R^5 groups are those wherein R^5 is C_{1-4} alkyl, phenyl, thienyl, furanyl, 5 isoxazolyl, pyridyl, cyclopentyl, cyclohexyl, benzothienyl, dihydrobenzofuranyl, phenyl- CH_2 -, furanyl- CH_2 - or - XR^6 .

Most preferably, R^5 is phenyl- CH_2 -, furanyl- CH_2 -, -C(O)-C(O)-thienyl or - XR^6 . Examples of most preferred R^5 groups are those wherein R^5 is phenyl- CH_2 -, furanyl- CH_2 - or - XR^6 .

10 Typically, X is -CO-, -S(O)- or -S(O)₂⁻. Preferably, X is -CO- or -S(O)₂⁻.

When R^6 is a group -NR' R'' and either R' or R'' includes an aryl, heteroaryl, carbocyclyl or heterocyclyl moiety it is typically unsubstituted or substituted by 1, 2 or 3 substituents selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, 15 C_{1-6} alkylthio, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, nitro and cyano. Preferably, the aryl, heteroaryl, carbocyclyl or heterocyclyl moiety is unsubstituted or substituted by 1 or 2 substituents selected from fluorine, chlorine, bromine, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} haloalkyl, C_{1-4} haloalkoxy and nitro. An example of preferred substitution is when the aryl, heteroaryl, carbocyclyl or heterocyclyl moiety is 20 unsubstituted or substituted by 1 or 2 substituents selected from fluorine, chlorine, bromine, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl and nitro. More preferably, the aryl, heteroaryl, carbocyclyl or heterocyclyl moiety is unsubstituted or substituted by one or two substituents selected from fluorine, chlorine, bromine, C_{1-2} alkyl, C_{1-2} alkoxy, C_{1-2} alkylthio, C_{1-2} haloalkyl and nitro. An example of more preferred substitution is 25 when the aryl, heteroaryl, carbocyclyl or heterocyclyl moiety is unsubstituted or substituted by a single fluoro, chloro, methyl, methoxy or nitro substituent. When R' or R'' is a heteroaryl or heterocyclyl group, it is attached via a carbon atom.

Typically, R' and R'' are not both hydrogen. Typically, each R' and R'' is the same or different and represents hydrogen, C_{1-4} alkyl, aryl, heteroaryl, 30 carbocyclyl, aryl-(C_{1-4} alkyl)- or heteroaryl-(C_{1-4} alkyl)-. Examples of typical R' and R'' groups are those wherein each R' and R'' is the same or different and represents hydrogen, C_{1-4} alkyl, phenyl, heteroaryl, for example thienyl, carbocyclyl, for

example cyclohexyl or cyclopentyl, or phenyl-(C₁₋₄ alkyl)-. Further examples of typical R' and R'' groups are those wherein each R' and R'' is the same or different and represents hydrogen, C₁₋₄ alkyl, phenyl, thienyl, cyclohexyl, cyclopentyl or phenyl-(CH₂)-. Preferably, each R' and R'' is the same or different and represents hydrogen,

5 C₁₋₄ alkyl, phenyl, phenyl-CH₂-, cyclohexyl or cyclopentyl. More preferably, one of R' and R'' represents hydrogen. Most preferably, one of R' and R'' is hydrogen and the other is C₁₋₄ alkyl, phenyl, phenyl-CH₂-, cyclohexyl or cyclopentyl. As an additional preference, one of R' and R'' is hydrogen and the other is C₁₋₄ alkyl, phenyl, thienyl or phenyl-CH₂-.

10 Typically, R⁶ is C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C₁₋₄ alkyl)-, heteroaryl-(C₁₋₄ alkyl)-, carbocyclyl-(C₁₋₄ alkyl)-, heterocyclyl-(C₁₋₄ alkyl)-, aryl-(C₁₋₄ hydroxyalkyl)-, heteroaryl-(C₁₋₄ hydroxyalkyl)-, carbocyclyl-(C₁₋₄ hydroxyalkyl)-, heterocyclyl-(C₁₋₄ hydroxyalkyl)-, aryl-(C₁₋₄ alkyl)-O-, heteroaryl-(C₁₋₄ alkyl)-O-, carbocyclyl-(C₁₋₄ alkyl)-O-, heterocyclyl-(C₁₋₄ alkyl)-O- or -NR'R'' wherein R' and R'' are as defined above. Examples of typical R⁶ groups are those wherein R⁶ is C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C₁₋₄ alkyl)-, heteroaryl-(C₁₋₄ alkyl)-, carbocyclyl-(C₁₋₄ alkyl)-, heterocyclyl-(C₁₋₄ alkyl)- or -NR'R'' wherein R' and R'' are as defined above.

15 Preferably, R⁶ is C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, aryl, for example phenyl, naphthyl, dihydrobenzofuranyl, benzodioxinyl, 9H-fluoren-9-onyl and indolyl, heteroaryl, for example thienyl, furanyl, oxazolyl, isoxazolyl, pyrazolyl, pyridyl, benzothienyl and benzofuranyl, carbocyclyl, for example cyclopentyl and cyclohexyl, heterocyclyl, for example piperazinyl, piperidinyl, morpholinyl and 1H-25 benzo[d]imidazol-2(3H)-onyl, phenyl-(C₁₋₂ alkyl)-, phenyl-(C₁₋₂ alkyl)-O-, phenyl-(C₁₋₂ hydroxyalkyl)-, heteroaryl-(C₁₋₂ hydroxyalkyl)-, heteroaryl-(C₁₋₂ alkyl)- or -NR'R'' wherein R' and R'' are as defined above. Examples of preferred R⁶ groups are those wherein R⁶ is C₁₋₄ alkyl, aryl, for example phenyl and dihydrobenzofuranyl, heteroaryl, for example thienyl, furanyl, isoxazolyl, pyridyl and benzothienyl,

30 carbocyclyl, for example cyclopentyl and cyclohexyl, heterocyclyl, for example N-heterocyclyl, phenyl-(C₁₋₂ alkyl)-, for example benzyl, heteroaryl-(C₁₋₂ alkyl)- or -NR'R'' wherein R' and R'' are as defined above.

More preferably, R^6 is C_{1-4} alkyl, C_{1-4} alkoxy, phenyl, naphthyl, dihydrobenzofuranyl, benzodioxinyl, 9H-fluoren-9-onyl, indolyl, thienyl, furanyl, oxazolyl, isoxazolyl, pyrazolyl, pyridyl, benzothienyl, benzofuranyl, cyclopentyl, cyclohexyl, piperazinyl, piperidinyl, morpholinyl, phenyl-(C_{1-2} alkyl)-, phenyl- CH_2 -
5 $CH(OH)$ -, phenyl- $CH(OH)$ - CH_2 -, phenyl-(C_{1-2} alkyl)- O -, 1*H*-benzo[*d*]imidazol-2(3*H*)-onyl or - $NR' R''$ wherein R' and R'' are as defined above. Example of most preferred R^6 groups are those wherein R^6 is C_{1-4} alkyl, phenyl, thienyl, furanyl, pyridyl, cyclopentyl, cyclohexyl, benzothienyl, dihydrobenzofuranyl, isoxazolyl, piperidinyl, for example N-piperidinyl, morpholinyl, for example N-morpholinyl,
10 piperazinyl, for example N-piperazinyl, or - $NR' R''$ wherein R' and R'' are as defined above.

Preferred compounds of the invention are those in which:

- R^1 is C_{1-6} alkyl or aryl;
- R^2 is hydrogen or C_{1-4} alkyl;
- 15 - R^3 is halogen, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, amino, mono(C_{1-4} alkyl)amino or di(C_{1-4} alkyl)amino or, preferably, R^3 is fluorine, chlorine, bromine, C_{1-2} alkyl, C_{1-2} alkoxy, C_{1-2} alkylthio, C_{1-2} haloalkyl, C_{1-2} haloalkoxy, amino, mono(C_{1-2} alkyl)amino or di (C_{1-2} alkyl)amino;
- n is 0, 1 or 2;
- 20 - R^4 is hydrogen or C_{1-4} alkyl;
 R^5 is C_{1-6} alkyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-4} alkyl)-, heteroaryl-(C_{1-4} alkyl)-, carbocyclyl-(C_{1-4} alkyl)-, heterocyclyl-(C_{1-4} alkyl)-, aryl-C(O)-C(O)-, heteroaryl-C(O)-C(O)- or - XR^6 ;
- X is -CO-, -S(O)- or -S(O)₂-; and
- 25 - R^6 is C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-4} alkyl)-, heteroaryl-(C_{1-4} alkyl)-, carbocyclyl-(C_{1-4} alkyl)-, heterocyclyl-(C_{1-4} alkyl)-, aryl-(C_{1-4} hydroxyalkyl)-, heteroaryl-(C_{1-4} hydroxyalkyl)-, carbocyclyl-(C_{1-4} hydroxyalkyl)-, heterocyclyl-(C_{1-4} hydroxyalkyl)-, aryl-(C_{1-4} alkyl)-O-, heteroaryl-(C_{1-4} alkyl)-O-, carbocyclyl-(C_{1-4} alkyl)-O-,
30 heterocyclyl-(C_{1-4} alkyl)-O- or - $NR' R''$, wherein each R' and R'' is the same or different and represents hydrogen, C_{1-4} alkyl, aryl, heteroaryl, carbocyclyl, aryl-(C_{1-4} alkyl)- or heteroaryl-(C_{1-4} alkyl)-,

the aryl moiety in the R¹ group being unsubstituted or substituted by 1, 2 or 3 substituents selected from halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl or C₁₋₆ haloalkoxy;

the aryl and heteroaryl moieties in the groups R⁵ and R⁶ being unsubstituted or substituted by 1, 2 or 3 substituents selected from halogen, C₁₋₆ alkyl, C₂₋₇ acyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, nitro, cyano, carbamoyl, mono(C₁₋₆ alkyl)carbamoyl, di(C₁₋₆ alkyl)carbomyl, amino, mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, -CO₂R', -CONR'R'', -S(O)R', -S(O)₂R', -S(O)NR'R'', -S(O)₂NR'R'', -NH-S(O)₂R' or -NH-CO-R', wherein each R' and R'' is 10 the same or different and represents hydrogen or C₁₋₆ alkyl;

the carbocyclyl and heterocyclyl moieties in the groups R⁵ and R⁶ being unsubstituted or substituted by 1, 2 or 3 substituents selected from halogen, C₁₋₆ alkyl, C₂₋₇ acyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, nitro, cyano, carbamoyl, mono(C₁₋₆ alkyl)carbamoyl, di(C₁₋₆ alkyl)carbomyl, amino, 15 mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, oxo, -CO₂R', -CONR'R'', -S(O)R', -S(O)₂R', -S(O)NR'R'', -S(O)₂NR'R'', -NH-S(O)₂R' or -NH-CO-R', wherein each R' and R'' is the same or different and represents hydrogen or C₁₋₆ alkyl; and

the alkyl moieties in the aryl-(C₁₋₄ alkyl)-, heteroaryl-(C₁₋₄ alkyl)-, carbocyclyl-(C₁₋₄ alkyl)-, heterocyclyl-(C₁₋₄ alkyl)- groups of R⁶ being unsubstituted 20 or substituted by one or two hydroxy substituents.

Preferably, in these preferred compounds of the invention, the aryl, heteroaryl and carbocyclyl moieties in the groups R' and R'' are unsubstituted or substituted by 1, 2 or 3 substituents selected from halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, nitro and cyano.

25 Examples of preferred compounds of the invention are those wherein R¹, R², R³, R⁴ and n are as defined for the preferred compounds of the invention,

- R⁵ is C₁₋₆ alkyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C₁₋₄ alkyl)-, heteroaryl-(C₁₋₄ alkyl)-, carbocyclyl-(C₁₋₄ alkyl)-, heterocyclyl-(C₁₋₄ alkyl)- or -XR⁶;
- X is -CO-, -S(O)- or -S(O)₂;
- R⁶ is C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C₁₋₄ alkyl)-, heteroaryl-(C₁₋₄ alkyl)-, carbocyclyl-(C₁₋₄ alkyl)-, heterocyclyl-(C₁₋₄ alkyl)- or -NR'R'', wherein each R' and R'' is the same or

different and represents hydrogen, C₁₋₄ alkyl, aryl, heteroaryl, carbocyclyl, aryl-(C₁₋₄ alkyl)- or heteroaryl-(C₁₋₄ alkyl)-,

the aryl, heteroaryl, carbocyclyl and heterocyclyl moieties in the groups R⁵ and R⁶ being unsubstituted or substituted by 1, 2 or 3 substituents selected from 5 halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, nitro and cyano.

Further preferred compounds of the invention are those wherein:

- R¹ is C₁₋₂ alkyl or phenyl;
- R² is hydrogen or C₁₋₄ alkyl;
- 10 - R³ is methyl, trifluoromethyl, fluorine, chlorine or bromine;
- n is 0 or 1;
- R⁴ is hydrogen or C₁₋₂ alkyl;
- R⁵ is C₁₋₄ alkyl, aryl, for example phenyl and dihydrobenzofuranyl, heteroaryl, for example thienyl, furanyl, isoxazolyl, pyridyl and benzothienyl, 15 carbocyclyl, for example cyclopentyl and cyclohexyl, heterocyclyl, for example piperidinyl, morpholinyl and piperazinyl, phenyl-(C₁₋₂ alkyl)-, for example benzyl, heteroaryl-(C₁₋₂ alkyl)-, phenyl-C(O)-C(O)-, heteroaryl-C(O)-C(O)- or -XR⁶, provided that when R⁵ is heterocyclyl it is attached via a carbon atom;
- X is -CO-, -S(O)- or -S(O)₂-; and
- 20 - R⁶ is C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, aryl, for example phenyl, naphthyl, dihydrobenzofuranyl, benzodioxinyl, 9H-fluoren-9-onyl and indolyl, heteroaryl, for example thienyl, furanyl, oxazolyl, isoxazolyl, pyrazolyl, pyridyl, benzothienyl and benzofuranyl, carbocyclyl, for example cyclopentyl and cyclohexyl, heterocyclyl, for example piperazinyl, piperidinyl, morpholinyl and 1H-benzo[a]imidazol-2(3H)-onyl, phenyl-(C₁₋₂ alkyl)-, phenyl-(C₁₋₂ alkyl)-O-, phenyl-(C₁₋₂ hydroxyalkyl)-, heteroaryl-(C₁₋₂ hydroxyalkyl)-, heteroaryl-(C₁₋₂ alkyl)- or -NR'¹R''² wherein each R'¹ and R''² is the same or different and represents hydrogen, C₁₋₄ alkyl, phenyl, heteroaryl, for example thienyl, carbocyclyl, for example cyclohexyl or cyclopentyl, or phenyl-(C₁₋₄ alkyl)-,
- 25 - the phenyl moiety in the R¹ group being unsubstituted or substituted by one or two substituents selected from fluorine, chlorine, bromine, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ haloalkyl or C₁₋₄ haloalkoxy;

the aryl moieties in the groups R⁵ and R⁶ being unsubstituted or substituted by 1, 2 or 3 substituents selected from halogen, C₁₋₆ alkyl, C₂₋₇ acyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, amino, mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, nitro, cyano, -CO₂R', -S(O)R', -S(O)₂R' and -S(O)₂NR'R'', wherein each R' and R'' is the same or different and represents hydrogen or C₁₋₄ alkyl;

5 the heteroaryl moieties in the groups R⁵ and R⁶ being unsubstituted or substituted by 1, 2 or 3 substituents selected from halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, nitro and cyano; and

10 the carbocyclyl and heterocyclyl moieties in the groups R⁵ and R⁶ being unsubstituted or substituted by 1, 2 or 3 substituents selected from halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, nitro, cyano and oxo; and

15 the alkyl moiety in the phenyl-(C₁₋₂ alkyl)- and heteroaryl-(C₁₋₂ alkyl)- groups of R⁶ being unsubstituted or substituted by a single hydroxy substituent.

20 Preferably, in these further preferred compounds of the invention, the phenyl, heteroaryl and carbocyclyl moieties in the groups R' and R'' are unsubstituted or substituted by 1 or 2 substituents selected from fluorine, chlorine, bromine, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy and nitro.

Examples of further preferred compounds of the invention are those wherein R¹, R², R³, R⁴ and n are as defined for the further preferred compounds of the invention,

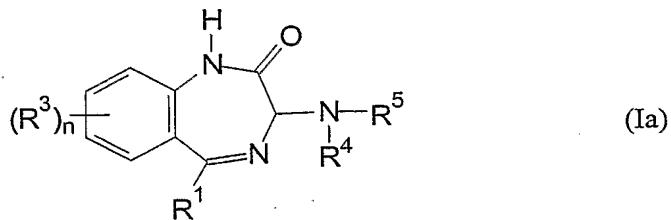
25 - R⁵ is C₁₋₄ alkyl, aryl, for example phenyl and dihydrobenzofuranyl, heteroaryl, for example thiényl, furanyl, isoxazolyl, pyridyl and benzothienyl, carbocyclyl, for example cyclopentyl and cyclohexyl, heterocyclyl, for example piperidinyl, morpholinyl and piperazinyl, phenyl-(C₁₋₂ alkyl)-, for example benzyl, heteroaryl-(C₁₋₂ alkyl)- or -XR⁶, provided that when R⁵ is heterocyclyl it is attached via a carbon atom;

30 - X is -CO-, -S(O)- or -S(O)₂-; and

- R^6 is C_{1-4} alkyl, aryl, for example phenyl and dihydrobenzofuranyl, heteroaryl, for example thienyl, furanyl, isoxazolyl, pyridyl and benzothienyl, carbocyclyl, for example cyclopentyl and cyclohexyl, heterocyclyl, for example N-heterocyclyl, phenyl-(C_{1-2} alkyl)-, for example benzyl, heteroaryl-(C_{1-2} alkyl)- or - $NR' R''$, wherein each R' and R'' is the same or different and represents hydrogen, C_{1-4} alkyl, cyclohexyl, cyclopentyl, phenyl or phenyl- CH_2- ,
- 5 the aryl, heteroaryl, carbocyclyl and heterocyclyl moieties in the groups R^5 and R^6 being unsubstituted or substituted by 1 or 2 substituents selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} haloalkyl, C_{1-6} haloalkoxy,
- 10 mono(C_{1-6} alkyl)amino, di(C_{1-6} alkyl)amino, nitro and cyano.

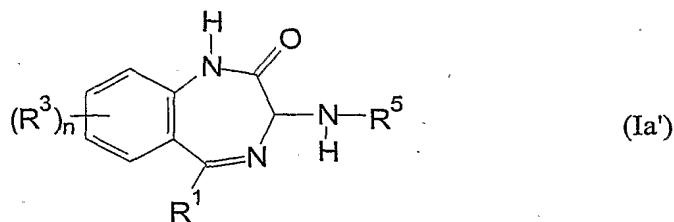
As a further preference, in these further preferred compounds of the invention, the cyclohexyl, cyclopentyl and phenyl moieties in the groups R' and R'' are unsubstituted or substituted by 1 or 2 substituents selected from fluorine, chlorine, bromine, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl and nitro.

- 15 Particularly preferred compounds of the invention are compounds of formula (Ia) are pharmaceutically acceptable salts thereof



- 20 wherein:
 - R^1 is phenyl or methyl;
 - R^3 is methyl or chlorine;
 - n is 0 or 1;
 - R^4 is hydrogen or methyl;
 - R^5 is phenyl- CH_2- , furanyl- CH_2- , thienyl-C(O)-C(O)- or - XR^6 ;
 - X is -CO- or -S(O)2-; and
 - R^6 is C_{1-4} alkyl, C_{1-4} alkoxy, phenyl, naphthyl, dihydrobenzofuranyl, benzodioxinyl, 9H-fluoren-9-onyl, indolyl, thienyl, furanyl, oxazolyl, isoxazolyl,
- 25

pyrazolyl, pyridyl, benzothienyl, benzofuranyl, cyclopentyl, cyclohexyl, piperazinyl, piperidinyl, morpholinyl, phenyl-(C₁₋₂ alkyl)-, phenyl-CH₂-CH(OH)-, phenyl-CH(OH)-CH₂-, phenyl-(C₁₋₂ alkyl)-O-, 1*H*-benzo[*d*]imidazol-2(3*H*)-onyl or -NR' R''
wherein each R' and R'' is the same or different and represents hydrogen, C₁₋₄ alkyl,
5 phenyl, thienyl, cyclohexyl, cyclopentyl or phenyl-(CH₂)-,
the phenyl moiety in the group R¹ being unsubstituted or substituted by a single fluorine, chlorine, C₁₋₂ alkyl, C₁₋₂ alkoxy, C₁₋₂ alkylthio, C₁₋₂ haloalkyl or C₁₋₂ haloalkoxy substituent;
the aryl moieties in the groups R⁵ and R⁶ being unsubstituted or substituted
10 by 1,2 or 3 substituents selected from fluorine, chlorine, bromine, iodine, C₁₋₄ alkyl, C₂₋₄ acyl, hydroxy, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, amino, mono(C₁₋₄ alkyl)amino, di(C₁₋₄ alkyl)amino, nitro, -CO₂R', -S(O)₂R' and -S(O)₂NH₂, wherein R' represents C₁₋₂ alkyl;
the heteroaryl moieties in the groups R⁵ and R⁶ being unsubstituted or
15 substituted by 1 or 2 substituents selected from fluorine, chlorine, bromine, C₁₋₂ alkyl, C₁₋₂ haloalkyl and di(C₁₋₂ alkyl)amino; and
the heterocyclyl and carbocyclyl moieties in the R⁶ group being unsubstituted or substituted by 1 or 2 substituents selected from fluorine, chlorine, bromine, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl and nitro.
20 Examples of particularly preferred compounds of formula (Ia) are compounds of formula (Ia') pharmaceutically acceptable salts thereof



wherein:

25 - R¹ is phenyl or methyl;
- R³ is chlorine;
- n is 0 or 1;
- R⁵ is phenyl-CH₂-, furanyl-CH₂- or -XR⁶;

- X is -CO- or -S(O)₂-; and
- R⁶ is C₁₋₄ alkyl, phenyl, thienyl, furanyl, pyridyl, cyclopentyl, cyclohexyl, benzothienyl, dihydrobenzofuranyl, isoxazolyl, piperidinyl, for example N-piperidinyl, morpholinyl, for example N-morpholinyl, piperazinyl, for example

5 N-piperazinyl, or -NR'R'', wherein each R' and R'' is the same or different and represents hydrogen, C₁₋₄ alkyl, cyclohexyl, cyclopentyl, phenyl or phenyl-CH₂-, the phenyl, thienyl, furanyl, pyridyl, cyclopentyl, cyclohexyl, benzothienyl, dihydrobenzofuranyl, isoxazolyl, piperidinyl, morpholinyl and piperazinyl moieties in the groups R⁵ and R⁶ being unsubstituted or substituted by 1 or 2 substituents

10 selected from fluorine, chlorine, bromine, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl and nitro.

Preferably, in these particularly preferred compounds of the invention, the cyclohexyl, cyclopentyl and phenyl moieties of the groups R' and R'' are unsubstituted or substituted by a single fluoro, chloro, methyl, methoxy or nitro substituent.

15 Compounds of the formula (I) containing one or more chiral centre may be used in enantiomerically or diastereoisomerically pure form, or in the form of a mixture of isomers. For the avoidance of doubt, the chemical structures depicted herein are intended to embrace all stereoisomers of the compounds shown, including 20 racemic and non-racemic mixtures and pure enantiomers and/or diastereoisomers.

Preferred compounds of the invention are optically active isomers. Thus, for example, preferred compounds of formula (I) containing only one chiral centre include an R enantiomer in substantially pure form, an S enantiomer in substantially pure form and enantiomeric mixtures which contain an excess of the R 25 enantiomer or an excess of the S enantiomer. For the avoidance of doubt, the compounds of the formula (I) can, if desired, be used in the form of solvates.

As used herein, a pharmaceutically acceptable salt is a salt with a pharmaceutically acceptable acid or base. Pharmaceutically acceptable acids include both inorganic acids such as hydrochloric, sulphuric, phosphoric, diphosphoric, 30 hydrobromic or nitric acid and organic acids such as citric, fumaric, maleic, malic, ascorbic, succinic, tartaric, benzoic, acetic, methanesulphonic, ethanesulphonic, benzenesulphonic or p-toluenesulphonic acid. Pharmaceutical acceptable bases

include alkali metal (e.g. sodium or potassium) and alkaline earth metal (e.g. calcium or magnesium) hydroxides and organic bases such as alkyl amines, aralkyl amines or heterocyclic amines.

Particularly preferred compounds of the invention include:

- 5 N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-acetamide;
1,1-Diethyl-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea;
N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-propionamide;
N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-butyramide;
N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-isobutyramide;
- 10 2,2-Dimethyl-N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-propionamide;
Cyclopentanecarboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
Cyclohexanecarboxylic acid 2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
- 15 3-Methoxy N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;
4-Methoxy N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;
- 20 2-Methoxy N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;
N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-3-trifluoromethyl-benzamide;
N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;
- 25 Thiophene-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-3-amide;
Furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
Piperidine-1-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
- 30 Morpholine-4-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;

4-Nitro- N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;
3-Nitro- N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;
4-Methyl-piperazine-1-carboxylic acid -(2-oxo-5-phenyl-2,3-dihydro-1H-
benzo[e][1,4]diazepin-3-yl)-amide;

5 3,4-Dichloro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-
benzamide;
N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-trifluoromethyl-
benzamide;
4-Bromo-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-
10 benzamide;
2-Methyl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-
benzamide;
2-Chloro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-
benzamide;

15 2-Nitro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;
2-Methoxy-4-nitro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-
benzamide;
(S)-2-Methoxy-4-nitro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-
yl)-benzamide

20 Benzo[b]thiophene-3-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-
benzo[e][1,4]diazepin-3-yl)-amide;
2,3-Dihydro-benzofuran-5-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-
benzo[e][1,4]diazepin-3-yl)-amide;
Isoxazole-5-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-
25 3-yl)-amide;

Benzo[b]thiophene-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-
benzo[e][1,4]diazepin-3-yl)-amide;
Thiophen-3-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-
3-yl)-amide;

30 N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-isonicotinamide;
N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-nicotinamide;
N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-

methanesulfonamide;

Propane-1-sulfonic acid-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;

Butane-1-sulfonic acid-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;

5 2-Bromo-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzenesulfonamide;

3-Bromo-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzenesulfonamide;

10 4-Bromo-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzenesulfonamide;

2-Fluoro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzenesulfonamide;

3-(2-Nitro-benzylamino)-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one;

15 3-(3-Nitro-benzylamino)-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one;

3-(4-Nitro-benzylamino)-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one;

3-(2-Methoxy-benzylamino)-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one;

3-(3-Methoxy-benzylamino)-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one;

5-Phenyl-3-(2-trifluoromethyl-benzylamino)-1,3-dihydro-benzo[e][1,4]diazepin-2-

20 one;

5-Phenyl-3-(3-trifluoromethyl-benzylamino)-1,3-dihydro-benzo[e][1,4]diazepin-2-one;

5-Phenyl-3-(4-trifluoromethyl-benzylamino)-1,3-dihydro-benzo[e][1,4]diazepin-2-one;

25 3-[(Furan-2-ylmethyl)-amino]-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one;

N-(7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-acetamide;

N-(7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-isobutyramide;

N-(7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-

30 methanesulfonamide;

Furan-2-carboxylic acid (7-chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;

Thiophene-2-carboxylic acid (7-chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;

Cyclohexanecarboxylic acid (7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;

5 N-(7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-methoxy-benzamide;

N-(7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-4-methoxy-benzamide;

10 N-(7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-nitro-benzamide;

2-(2-Methoxy-phenyl)N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-acetamide;

2-(3-Methoxy-phenyl)N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-acetamide;

15 2-(4-Methoxy-phenyl)N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-acetamide;

2-(4-Nitro-phenyl)N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-acetamide;

2-(3-Nitro-phenyl)N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-acetamide;

20 N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-(2-trifluoromethyl-phenyl)-acetamide;

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-(3-trifluoromethyl-phenyl)-acetamide;

25 N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-(4-trifluoromethyl-phenyl)-acetamide;

1-(2-Methoxy-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea;

1-(2-Nitro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea;

30 1-(2-Chloro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea;

1-(4-Chloro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea;

1-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-3-p-tolyl-urea;

1-(2-Fluoro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea;

5 1-(4-Fluoro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea;

(S)-1-(2-Fluoro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea;

10 4-Methanesulfonyl-2-methoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

(S)- 4-Methanesulfonyl-2-methoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

5-Acetyl-2-ethoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-

15 benzamide;

(S)- 5-Acetyl-2-ethoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

6-Fluoro-4H-benzo[1,3]dioxine-8-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;

20 (S)- 6-Fluoro-4H-benzo[1,3]dioxine-8-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;

(S)-2-Methoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-4-trifluoromethyl-benzamide;

2,4,5-Trifluoro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-

25 benzamide;

(S)-2,4,5-Trifluoro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

2-Hydroxy- N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

30 (S)-2-Hydroxy- N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

1H-Indole-7-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-

benzo[e][1,4]diazepin-3-yl)-amide;
(S)-1H-Indole-7-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-
benzo[e][1,4]diazepin-3-yl)-amide;
3-Methoxy-naphthalene-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-
5 benzo[e][1,4]diazepin-3-yl)-amide;
(S)-3-Methoxy-naphthalene-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-
benzo[e][1,4]diazepin-3-yl)-amide;
N-[7-Chloro-5-(2-fluoro-phenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepine-3-
yl]-4-methoxoy-benzamide;
10 1-(2-Fluoro-benzyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-
urea;
1-(4-Methoxy-benzyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-
yl)-urea;
1-(3-Methyl-benzyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-
15 yl)-urea;
1-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-3-(4-
trifluoromethyl-phenyl)-urea;
4-Chloro-2-methoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-
yl)-benzamide;
20 4-Methoxy-3-nitro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-
yl)benzamide;
3-Methoxy-2-nitro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-
benzamide;
5-Chloro-2-methoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-
25 yl)benzamide;
5-Fluoro-2-methoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-
yl)-benzamide;
2-Methoxy-4-nitro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-
benzamide;
30 5-Methoxy-2-nitro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-
benzamide;
3-Methoxy-4-nitro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-

benzamide;

3-(2-Methoxy-phenyl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)propionamide;

3-(3-Methoxy-phenyl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-propionamide;

5 3-(4-Methoxy-phenyl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-propionamide;

N-[5-(3-Chloro-phenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-2-methoxy-benzamide;

10 N-[5-(3-Chloro-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-4-methoxy-benzamide;

N-[5-(3-Chloro-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-2-nitro-benzamide;

N-[5-(3-Chloro-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-15 yl]-4-nitro-benzamide;

4-Methoxy-N-[2-oxo-5-(4-trifluoromethyl-phenyl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-benzamide;

2-Methoxy-N-[2-oxo-5-(3-trifluoromethyl-phenyl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-benzamide;

20 4-Methoxy-N-[2-oxo-5-(3-trifluoromethyl-phenyl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-benzamide;

2-Ethoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

2,4-Dimethoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-25 benzamide;

2-Bromo-5-methoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

2-Methoxy-N-[5-(3-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-benzamide

30 N-[5-(3-Methoxy-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-4-nitro-benzamide;

2-Methoxy-N-(8-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-

yl)-benzamide;

2-Chloro-4-methanesulfonyl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

2-Dimethylamino-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

5 (2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-carbamic acid benzyl ester;

1-(3,5-Dimethyl-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea;

10 1-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-3-(4-trifluoromethoxy-phenyl)-urea;

1-(4-Bromo-2-trifluoromethyl-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea;

1-(4-Bromo-benzyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea;

15 1-(2,3-Dichloro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea;

1-(2,6-Dimethyl-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea;

20 1-(2-Chloro-6-methyl-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea;

1-(4-Nitro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea;

1-(2-Methylsulfanyl-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea;

25 1-(2,6-Dichloro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea;

5-tert-Butyl-2-methoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

30 2,5-Dimethoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

1-(2,6-Difluoro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-

yl)-urea;

1-(3-Fluoro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea;

1-(3-Methoxy-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea;

1-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-3-(3-trifluoromethyl-phenyl)-urea;

1-(3-Chloro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea;

10 2-Methoxy-4-methylsulfanyl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

4-Methanesulfonyl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)terephthalamic acid

15 methyl ester;

2-Fluoro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

2,6-Difluoro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

20 N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-propoxy-benzamide;

2-Iodo-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

3-Methoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-terephthalamic acid methyl ester;

25 4-Amino-5-chloro-2-methoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

1-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-3-m-tolyl-urea;

2-Methylsulfanyl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

30 2-Methoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-5-sulfamoyl-benzamide;

2-Hydroxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-3-

phenyl-propionamide

3-Hydroxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-3-phenyl-propionamide ;

3-(2-Fluoro-phenyl)-1-methyl-1-(2-oxo-5-phenyl-2,3-dihydro-1H-5 benzo[e][1,4]diazepin-3-yl)-urea;

2-Methoxy-N-methyl-4-nitro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

1-tert-Butyl-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea;

1-Cyclohexyl-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea;

10 1-Ethyl-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea;

1-Butyl-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea;

4,5-Dimethyl-furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-15 benzo[e][1,4]diazepin-3-yl)amide;

Piperidine-1-carboxylic acid (7-chloro-2-oxo-5-phenyl-2,3-dihydro-1H-15 benzo[e][1,4]diazepin-3-yl)-amide;

N-[5-(3-Chloro-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]acetamide;

N-[5-(3-Chloro-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-isobutyramide;

20 Furan-2-carboxylic acid [5-(3-chloro-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-amide;

Thiophene-2-carboxylic acid [5-(3-chloro-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-amide;

Cyclohexanecarboxylic acid [5-(3-chloro-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-25 benzo[e][1,4]diazepin-3-yl]-amide;

Piperidine-1-carboxylic acid [5-(3-chloro-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-amide;

N-[5-(3-Chloro-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]isonicotinamide;

30 5-Methyl-furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;

Pyrazine-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-

3-yl)-amide;

N-[5-(3-Methoxy-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-isobutyramide;

Thiophene-2-carboxylic acid [5-(3-methoxy-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-amide;

5 Cyclohexanecarboxylic acid [5-(3-methoxy-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-amide;

Piperidine-1-carboxylic acid [5-(3-methoxy-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-amide;

10 Piperidine-4-carboxylic acid [5-(3-methoxy-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-amide;

Cyclohexanecarboxylic acid (8-chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;

Thiophene-2-carboxylic acid (8-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-15 benzo[e][1,4]diazepin-3-yl)-amide;

1-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-3-thiophene-2-yl-urea;

1-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-3-thiophene-3-yl-urea;

20 Pyridine-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;

1H-Pyrazole-4-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;

6-Dimethylamino-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-25 nicotinamide;

2-Ethoxy-naphthalene-1-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;

9-Oxo-9H-fluorene-1-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;

30 2-Oxo-2,3-dihydro-benzoimidazole-1-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;

(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)carbamic acid tert-

butyl ester;

(S)-4,5-Dibromo-furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;

(S)-Benzofuran-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;

5 (2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-carbamic acid methyl ester;

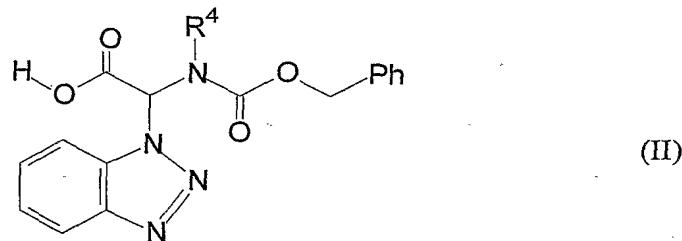
(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-carbamic acid ethyl ester;

10 (2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-carbamic acid isobutyl ester; and

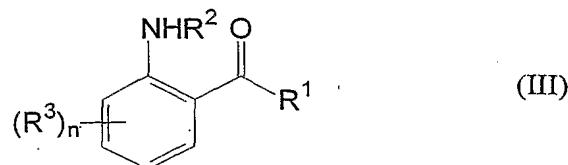
2-Oxo-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-thiophene-2-yl-acetamide,

and pharmaceutically acceptable salts thereof.

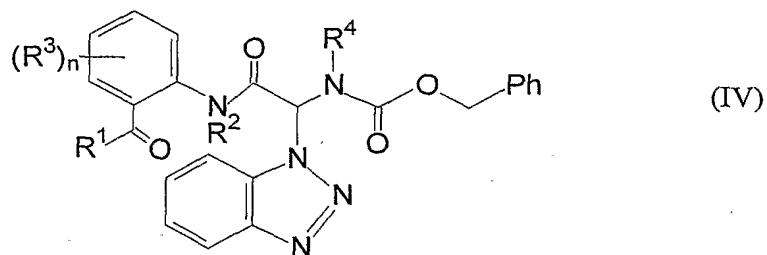
15 Compounds of formula (I) may be prepared by reacting glyoxylic acid ($\text{HCO-CO}_2\text{H}$), benzotriazole and an appropriate benzyl carbamate at reflux in toluene, under Dean-Stark conditions giving the key protected amino acid of formula (II)



20 The thus obtained amino acid of formula (II) can then be reacted with a suitable chlorinating agent, such as oxalyl chloride, followed by reaction with a 2-aminobenzophenone of formula (III)

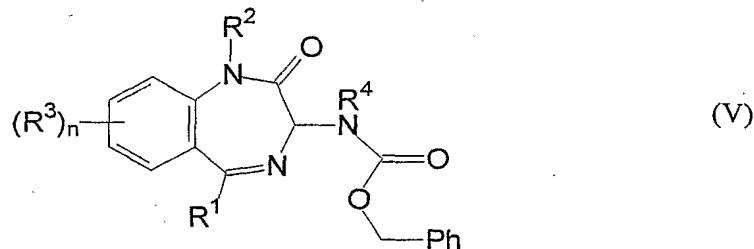


to give the intermediate amide of formula (IV)

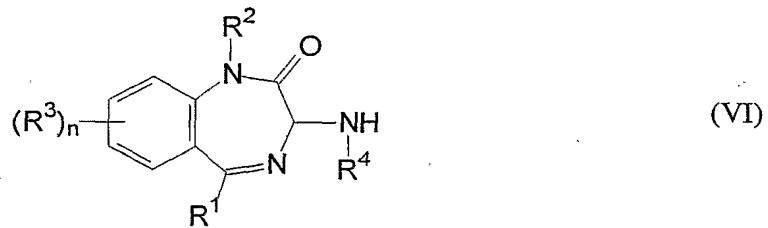


which need not be characterized.

The compound of formula (IV) can then be subjected to ammonolysis
5 followed by ring closure in acetic acid containing ammonium acetate to obtain the
protected benzodiazepine of formula (V)



The compound of formula (V) can then be deprotected using hydrogen bromide in acetic acid to yield the deprotected amine of formula (VI).



10

Compounds of formula (I), in which R⁵ is XR⁶ and X is -CO- can be prepared by reacting a compound of formula (VI), as defined above, with an acid anhydride in a suitable solvent, preferably pyridine at ambient temperature, or with an acid chloride in a suitable solvent in the presence of a base, preferably in THF at 15 ambient temperature with triethylamine present. Alternatively, the compounds can

be produced by reaction of a compound of formula (VI) with an acid in a suitable solvent in the presence of a base and a coupling agent, preferably in THF at ambient temperature with triethylamine and *O*-benzotriazol-1-yl-N, N, N', N'-tetramethyluronium hexafluorophosphate (HBTU) present.

5 If the acid chloride used is an amino carbonyl chloride, the compound of formula (I) is a tertiary urea. In the case where R⁶ is NH-R', such compounds may be prepared by the reaction of a compound of formula (VI) with an isocyanate. This reaction is preferably carried out in THF at ambient temperature. Alternatively, the isocyanate may be prepared *in situ* from the relevant amine and phosgene, in the
10 presence of a base, usually triethylamine, again in THF.

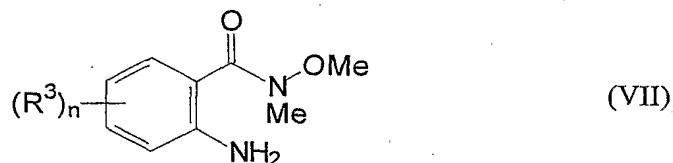
Compounds of formula (I), in which R⁵ is -XR⁶ and X is -S(O)₂- may be prepared by the reaction of a compound of formula (VI) with a suitable sulfonyl chloride. Similarly, compounds of formula (I), in which R⁵ is XR⁶ and X is -S(O)- may be prepared by the reaction of a compound of formula (VI) with a suitable
15 sulfinyl chloride

Compounds of formula (I) in which R⁵ is not XR⁶ may be prepared by known methods. For example, a compound of formula (VI) can be reacted with a compound of formula R⁵-L, wherein L is a leaving group such as a chlorine atom, a mesylate group or a triflate group. When R⁵ is aryl or heteroaryl, L can be -B(OH)₂
20 and the reaction may take place in the presence of copper acetate. Such boronic acid coupling reactions will, of course, be familiar to those of skill in the art. Compounds wherein R⁵ is aryl or heteroaryl may also be prepared by way of a Buchwald reaction or by reaction of a compound of formula (VI) with an appropriate fluoroaryl or fluoroheteroaryl compound. Compounds wherein R⁵ is a heteroaryl group may also
25 be prepared by reaction of a compound of formula (VI) with a suitable chloroheteroaryl or bromoheteroaryl compound. Compounds wherein R⁵ is a carbocyclyl group may also be prepared by known methods, for example a compound wherein R⁵ is cyclohexyl may be prepared by the reaction of a compound of formula (VI) with cyclohexanone in the presence of a reducing agent.

30 Compounds of formula (I) in which the R⁵ group is aryl-(C₁₋₆ alkyl)-, heteroaryl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆ alkyl)-, heterocyclyl-(C₁₋₆ alkyl)- can also be prepared by the reaction of a compound of formula (VI) with an aldehyde in the

presence of a reducing agent. Preferably, such reactions between compounds of formula (VI) and aldehydes are carried out in a mixture of dichloromethane and acetic acid in the presence of sodium (triacetoxy)borohydride at ambient temperature.

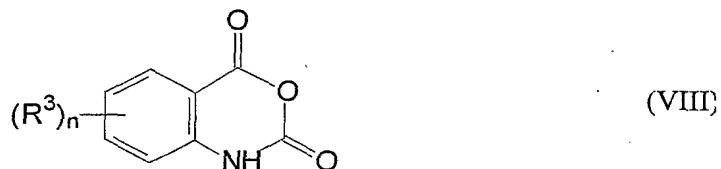
5 In the preparation of the benzodiazepine skeleton, commercially available aminobenzophenone compounds of formula (III) can be used where possible. Compounds of formula (III) which are not commercially available can be prepared by known methods, for example by reaction of a Weinreb type amide of formula (VII)



10

with a group R¹-Li or a Grignard reagent such as R¹-MgBr. Preferably this reaction is carried out in THF at -100°C.

15 Compounds of formula (VII) are known compounds or can be prepared by analogy with known methods. For example, they can be prepared from the reaction of isatoic anhydrides of formula (VIII)



with N,O-dimethyl hydroxylamine under standard reaction conditions.

The starting materials of formula (II), (III), (VII), and (VIII) are known compounds, or may be prepared by analogy with known methods.

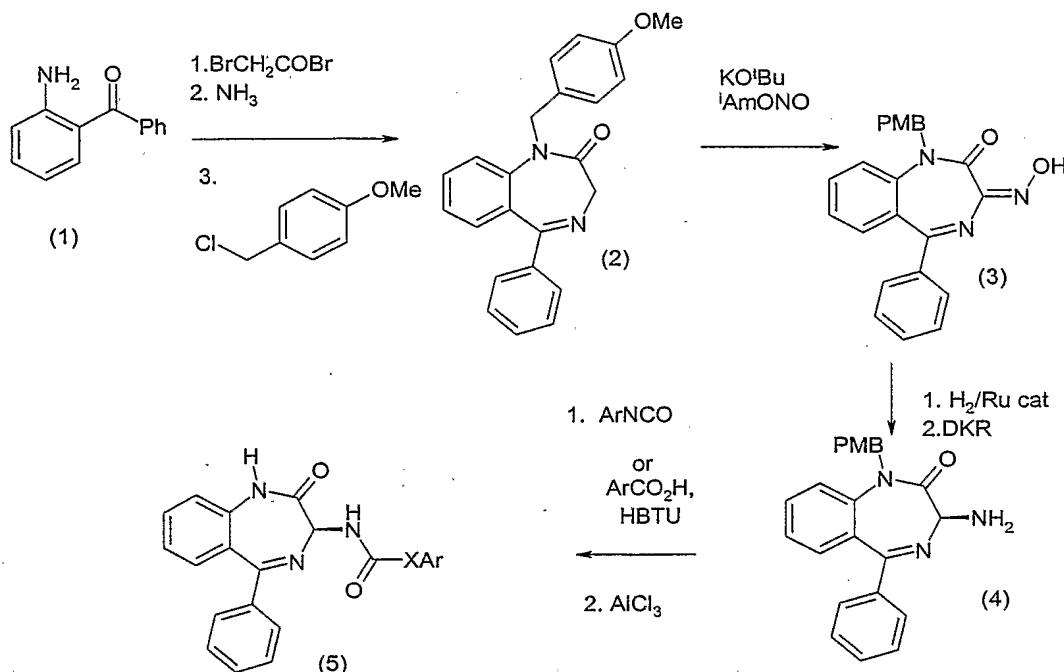
20 Further synthetic manipulation of the thus obtained compounds of formula (I) may be carried out by conventional methods to achieve further compounds of formula (I). The benzodiazepines of formula (I) can be saponified by treatment with an appropriate acid or base.

Although the described route to the claimed compounds provides an

adequate synthesis for laboratory scale preparations, an alternative route was sought which has potential as a manufacturing route. The same starting material (2-amino-benzophenone) (1) is used in both, however in the alternative route, the benzodiazepine ring system is formed by reaction initially with bromoacetyl bromide 5 (or an equivalent reagent) followed by ring closure with ammonia. These reactions are carried out in a suitable solvent, such as dichloromethane, and at a suitable temperature which may range from -20 to 150°C. In order to protect the NH functionality, at this stage the unsubstituted benzodiazepine is reacted with a base, and an alkylating agent. For instance sodium hydride in DMF followed by addition 10 of 4-methoxy-benzyl chloride gives rise to the intermediate (2) shown below. Further reaction of this material with a base (e.g. potassium tert-butoxide) in a suitable solvent (e.g. THF or DMF) followed by quenching with isoamyl nitrite (or an alternative similar reagent) furnishes the oxime intermediate (3) which may be converted into the racemic primary amine by methods which include the use of 15 hydrogen and a suitable catalyst. This amine then undergoes a Dynamic Kinetic Resolution (DKR) procedure by which the racemic amine in the presence of a suitable optically active acid, and a suitable aldehyde gives rise to precipitation of the salt of the desired (S)-amine (4) in good yield and exceptionally high enantiomeric excess. A suitable acid for this conversion can be e.g. Camphorsulfonic acid, Boc- 20 phenyl alanine or the like, and a suitable aldehyde may be a benzaldehyde such as 3,5-dichloro salicylaldehyde.

The optically amine thus formed may then be transformed into a desired derivative, such as an amide or urea. The amide formations may be carried out using a suitable carboxylic acid and a coupling reagent, or a carbonyl chloride or 25 other suitable reagent, and the ureas prepared using either a suitable isocyanate, or alternatively reaction with phosgene followed by a suitable amine.

These derivatives thus formed may then have the protecting group removed. This may be carried out in the presence of a Lewis Acid, such as aluminium chloride, boron trifluoride, titanium tetrachloride, or the like. These 30 reactions are carried out in a suitable inert solvent, such as dichloromethane. Reaction temperatures may range from -20 to 150°C, but are typically carried out at room temperature or below.



5 As explained above, the compounds of the invention are active against RSV. The present invention therefore provides a method for treating a patient suffering from or susceptible to an RSV infection, which method comprises administering to said patient an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

10 RSV is prevalent among children younger than two years of age. It is a particularly serious risk amongst any such children who suffer from chronic lung disease. Accordingly, the said medicament is typically for use in treating a patient who is a child under two years of age. Typically, said child suffers from chronic lung disease.

15 Further, anti-RSV prophylaxis is recommended for infants born at 32 weeks of gestation or earlier, until they reach 6 months of age. Accordingly, the said medicament is typically for use in preventing RSV infection in an infant less than 6 years of age, who was born after 32 weeks of gestation or less.

It has been shown that RSV infections are accompanied by 20 inflammatory reactions (Noah et al, Clinical Immunology 2000, Vol 97, 43-49). The

present invention also relates to a combination of a compound of formula (I), or a pharmaceutically acceptable salt thereof, with an anti-inflammatory compound and the use of such a combination in the treatment of RSV. Typically, said anti-inflammatory compound is a steroid, for example budesonide or fluticasone, a non-
5 steroid, for example a leukotriene antagonist, phosphodiesterase 4 inhibitor or TNF alpha inhibitor or an interleukin 8 or interleukin 9 inhibitor.

Thus, in one embodiment, a compound of formula (I), or a pharmaceutically acceptable salt thereof, is combined with a steroid antiinflammatory compound, for example budesonide or fluticasone. In a preferred
10 embodiment, the steroid is administered in low doses to minimize immuno-suppressant effects. In another embodiment a compound of formula (I), or a pharmaceutically acceptable salt thereof, is combined with a non-steroid anti-inflammatory compound, for example leukotriene antagonists such as Singulair (Merck) or Accolate (Astra Zeneca), phosphodiesterase 4 inhibitors such as
15 roflumilast (Altana), TNF alpha inhibitors such as Enbrel (Amgen), Remicade (Centocor), Humira (Abbott) or CDP870 (Celltech) or NSAIDS. In a further embodiment, a compound of formula (I) is combined with interleukin 8 or interleukin 9 inhibitors. The present invention thus also relates to a product containing a compound of formula (I), or a pharmaceutically acceptable salt thereof,
20 and an anti-inflammatory compound for simultaneous, separate or sequential use in the treatment of RSV.

The present invention also relates to a combination of a compound of formula (I), or a pharmaceutically acceptable salt thereof, with an anti-influenza compound and the use of such a combination in the treatment of concomitant RSV and influenza infections. The present invention thus also relates to a product containing a compound of formula (I), or a pharmaceutically acceptable salt thereof, and an anti-influenza compound for simultaneous, separate or sequential use in the treatmet of concomitant RSV and influenza infections.

It is a further surprising finding of the present invention that
30 compounds of the invention are active against human metapneumovirus, measles, parainfluenza viruses and mumps. The present invention thus provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the

manufacture of a medicament for use in the treatment of human metapneumovirus, measles, parainfluenza viruses and mumps. It is an additional surprising finding of the present invention that compounds of the invention are active against yellow fever virus (B5 strain), Dengue 2 virus and West Nile virus. The present invention thus

5 provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of yellow fever virus (B5 strain), Dengue 2 virus and West Nile virus.

The compounds of the invention may be administered in a variety of dosage forms. Thus, they can be administered orally, for example as tablets, troches, 10 lozenges, aqueous or oily suspensions, dispersible powders or granules. The compounds of the invention may also be administered parenterally, whether subcutaneously, intravenously, intramuscularly, intrasternally, transdermally or by infusion techniques. The compounds may also be administered as suppositories.

In a preferred embodiment, the compounds of the invention are 15 administered by intranasal or intrabronchial administration. The present invention also provides an inhaler or nebuliser containing a medicament which comprises (a) a benzodiazepine derivative of the formula (I), as defined above, or a pharmaceutically acceptable salt thereof, and (b) a pharmaceutically acceptable carrier or diluent.

The present invention also provides a pharmaceutical composition 20 containing such a benzodiazepine derivative, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

Said pharmaceutical composition typically contains up to 85 wt% of a compound of the invention. More typically, it contains up to 50 wt% of a compound of the invention. Preferred pharmaceutical compositions are sterile and pyrogen free. 25 Further, the pharmaceutical compositions provided by the invention typically contain a compound of the invention which is a substantially pure optical isomer.

The compounds of the invention are typically formulated for administration with a pharmaceutically acceptable carrier or diluent. For example, solid oral forms may contain, together with the active compound, diluents, e.g. 30 lactose, dextrose, saccharose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents; e.g. starches, arabic gums, gelatin, methylcellulose,

carboxymethylcellulose or polyvinyl pyrrolidone; disaggregating agents, e.g. starch, alginic acid, alginates or sodium starch glycolate; effervescent mixtures; dyestuffs; sweeteners; wetting agents, such as lecithin, polysorbates, laurylsulphates; and, in general, non toxic and pharmacologically inactive substances used in pharmaceutical 5 formulations. Such pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tableting, sugar coating, or film coating processes.

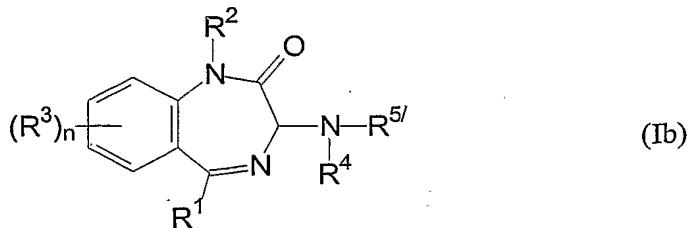
Liquid dispersions for oral administration may be syrups, emulsions and suspensions. The syrups may contain as carriers, for example, saccharose or 10 saccharose with glycerine and/or mannitol and/or sorbitol.

Suspensions and emulsions may contain as carrier, for example a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol. The suspension or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, 15 e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and if desired, a suitable amount of lidocaine hydrochloride.

Solutions for injection or infusion may contain as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions.

20 A therapeutically effective amount of a compound of the invention is administered to a patient. A typical dose is from about 0.001 to 50 mg per kg of body weight, according to the activity of the specific compound, the age, weight and conditions of the subject to be treated, the type and severity of the disease and the frequency and route of administration. Preferably, daily dosage levels are from 5 mg 25 to 2 g.

Certain benzodiazepine derivatives of the formula (I) are novel *per se*. The present invention includes these novel compounds and pharmaceutically acceptable salts thereof. The present invention therefore also provides compounds of formula (Ib) and pharmaceutically acceptable salts thereof



wherein:

- R^1 represents C_{1-6} alkyl, aryl or heteroaryl;
- R^2 represents hydrogen, C_{1-6} alkyl;
- 5 - each R^3 is the same or different and represents halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, amino, mono(C_{1-6} alkyl)amino, di(C_{1-6} alkyl)amino, nitro, cyano, $-CO_2R'$, $-CONR'R''$, $-NH-CO-R'$, $-S(O)R'$, $-S(O)_2R'$, $-NH-S(O)_2R'$, $-S(O)NR'R''$ or $-S(O)_2NR'R''$, wherein each R' and R'' is the same or different and represents hydrogen or C_{1-6} alkyl;
- 10 - n is from 0 to 3;
- R^4 represents hydrogen or C_{1-6} alkyl;
- $R^{5'}$ represents C_{3-6} alkyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6} alkyl)-, carbocyclyl-(C_{1-6} alkyl)-, heterocyclyl-(C_{1-6} alkyl)-, aryl-C(O)-C(O)-, heteroaryl-C(O)-C(O)-, carbocyclyl-C(O)-C(O)-, heterocyclyl-C(O)-C(O)- or $-X'$, provided that when $R^{5'}$ is heteroaryl it is not 2-quinaldyl or 6-chloro-pyrazinyl, when $R^{5'}$ is heteroaryl-(C_{1-6} alkyl)- it is not 2-indolylmethyl, 2-(3-indolyl)ethyl or 2-furanylmethyl, when $R^{5'}$ is aryl it is not unsubstituted phenyl and when $R^{5'}$ is aryl-(C_{1-6} alkyl)- it is not unsubstituted phenyl-(C_{1-2} alkyl)- or 4-chlorophenyl-(C_{2-3} alkyl)-;
- 15 - X' represents $-CO-R^{6'}$, $-S(O)-R^{6''}$ or $-S(O)_2-R^{6'''}$;
- R^6 represents C_1 alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6} alkyl)-, carbocyclyl-(C_{1-6} alkyl)-, heterocyclyl-(C_{1-6} alkyl)-, aryl-(C_{1-6} hydroxyalkyl)-, heteroaryl-(C_{1-6} hydroxyalkyl)-, carbocyclyl-(C_{1-6} hydroxyalkyl)-, heterocyclyl-(C_{1-6} hydroxyalkyl)-, aryl-(C_{1-6} alkyl)-O-, heteroaryl-(C_{1-6} alkyl)-O-, carbocyclyl-(C_{1-6} alkyl)-O-, heterocyclyl-(C_{1-6} alkyl)-O- or $-NR'R''$ wherein each R' and R'' is the same or different and represents hydrogen, C_{1-6} alkyl, carbocyclyl, heterocyclyl, aryl,

heteroaryl, aryl-(C₁₋₆ alkyl)-, heteroaryl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆ alkyl)- or heterocyclyl-(C₁₋₆ alkyl)-, provided that (a) when R^{6/} is aryl it is not unsubstituted naphthyl, unsubstituted phenyl, mono-halophenyl, 4-methylphenyl, 4-methoxyphenyl, 4-hydroxyphenyl, 4-trifluoromethylphenyl,

5 4-nitrophenyl, 4-cyanophenyl, 4-n-propylphenyl, 4-t-butylphenyl, 4-n-pentylphenyl, 4-dimethylaminophenyl, 4-methylthiophenyl, 3-trifluoromethylthiophenyl, 3,4-dimethoxyphenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 2,3,4,5,6-pentafluorophenyl, 4-chloro-2-aminophenyl or 4-1,1-dimethylethylphenyl, (b) when R^{6/} is heteroaryl it is not 2-pyrrolyl, 2-pyrazinyl, 2-quinaldyl, 2-quinoxalinyl, 1-methylindolonyl, 2-methyl-indolyl, 2-benzofuranyl, 2-benzothienyl, 3-thienyl, 3-indolyl, unsubstituted 2-indolyl, 5-fluoroindol-2-yl, 5-chloroindol-2-yl, 5-bromoindol-2-yl, 5-hydroxyindol-2-yl or 5-methoxyindol-2-yl, (c) when R^{6/} is aryl-(C₁₋₆ alkyl)- it is not 4-thianaphthene-(CH₂)-, unsubstituted phenyl-(CH₂)-, 4-trifluoromethylphenyl-(CH₂)-, unsubstituted phenyl-(CH₂)₃-,

10 15 monotrifluoromethylphenyl-(CH₂)₂-, 3-methoxyphenyl-(CH₂)₂-, 4-chloro-2-aminophenyl-(CH₂)₂-, 2,4-dichlorophenyl-(CH₂)₂-, monochlorophenyl-(CH₂)₂-, 2,4-trifluoromethyl phenyl-(CH₂)₂-, 4-cyanophenyl-(CH₂)₂- or 3-cyanophenyl-(CH₂)₂-,

(d) when R^{6/} is heteroaryl-(C₁₋₆ alkyl)- it is not indolyl-(CH₂)_x-, wherein x is 1, 2, 3, unsubstituted furanyl-(CH₂)₂-, unsubstituted thienyl-(CH₂)₃- (e) when R^{6/} is 20 carbocyclyl it is not cyclohexyl, (f) when R^{6/} is carbocyclyl-(C₁₋₆ alkyl)- it is not unsubstituted cyclohexyl-(CH₂)₁₋₃-, (g) when R^{6/} is heterocyclyl it is not N-pyrrolidinyl or 2-dihydrobenzofuranyl, (h) when R^{6/} is aryl-(C₁₋₆ alkyl)-O- it is not unsubstituted phenyl-(CH₂)-O-, and (i) when R' is hydrogen, R'' is not unsubstituted phenyl, 4-halophenyl, 3-halophenyl, methoxyphenyl, nitrophenyl, 2-chlorophenyl, 4-methylphenyl, dichlorophenyl, 3,5-dimethylphenyl, 3-methylphenyl, 3-cyanophenyl, 3-aminophenyl, 3-aminocarbonylphenyl, 3-benzoic acid, 3-benzoic acid ethyl ester, 6-amino-3-pyridyl, 5-(2-chloro)pyridyl, 5-(2-methoxy)pyridyl, 5-indanyl, unsubstituted cyclohexyl, 1,1-dimethylethyl, unsubstituted phenyl-CH₂-, unsubstituted naphthyl or benzotriazol-3-yl and when R' is methyl, R'' is not 25 30 cyclopropylbenzene;

- R^{6//} represents C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C₁₋₆ alkyl)-, heteroaryl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆

alkyl)-, heterocyclyl-(C₁₋₆ alkyl)-, aryl-(C₁₋₆ hydroxyalkyl)-, heteroaryl-(C₁₋₆ hydroxyalkyl)-, carbocyclyl-(C₁₋₆ hydroxyalkyl)-, heterocyclyl-(C₁₋₆ hydroxyalkyl)-, aryl-(C₁₋₆ alkyl)-O-, heteroaryl-(C₁₋₆ alkyl)-O-, carbocyclyl-(C₁₋₆ alkyl)-O-, heterocyclyl-(C₁₋₆ alkyl)-O- or -NR'¹R''² wherein each R' and R'' is the same or different and represents hydrogen, C₁₋₆ alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C₁₋₆ alkyl)-, heteroaryl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆ alkyl)- or heterocyclyl-(C₁₋₆ alkyl)-; and

- R^{6//} represents C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C₁₋₆ alkyl)-, heteroaryl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆ alkyl)-, heterocyclyl-(C₁₋₆ alkyl)-, heterocyclyl-(C₁₋₆ alkyl)-, aryl-(C₁₋₆ hydroxyalkyl)-, heteroaryl-(C₁₋₆ hydroxyalkyl)-, carbocyclyl-(C₁₋₆ hydroxyalkyl)-, heterocyclyl-(C₁₋₆ hydroxyalkyl)-, aryl-(C₁₋₆ alkyl)-O-, heteroaryl-(C₁₋₆ alkyl)-O-, carbocyclyl-(C₁₋₆ alkyl)-O-, heterocyclyl-(C₁₋₆ alkyl)-O- or -NR'¹R''² wherein each R' and R'' is the same or different and represents hydrogen, C₁₋₆ alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C₁₋₆ alkyl)-, heteroaryl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆ alkyl)- or heterocyclyl-(C₁₋₆ alkyl)-, provided that when R^{6//} is aryl it is not 4-methylphenyl, provided that the compound of formula (Ib) is not N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-acetamide.

Preferably, in the formula (Ib),

- each R³ is the same or different and represents halogen, hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, amino, mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, nitro, cyano, -CO₂R', -CONR'¹R''², -NH-CO-R', -S(O)R', -S(O)₂R', -NH-S(O)₂R' or -S(O)NR'¹R''², wherein each R' and R'' is the same or different and represents hydrogen or C₁₋₆ alkyl;

- R^{5/} represents C₂₋₆ alkyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C₁₋₆ alkyl)-, heteroaryl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆ alkyl)-, heterocyclyl-(C₁₋₆ alkyl)- or -X', provided that when R^{5/} is heteroaryl it is not 2-quinaldyl or 6-chloro-pyrazinyl and when R^{5/} is heteroaryl-(C₁₋₆ alkyl)- it is not 2-indolylmethyl or 2-(3-indolyl)ethyl;

- X' represents -CO-R^{6/}, -S(O)-R^{6//} or -S(O)₂-R^{6//};

- R^{6/} represents C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C₁₋₆ alkyl)-, heteroaryl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆

alkyl)-, heterocyclyl-(C₁₋₆ alkyl)- or -NR'¹R'' wherein each R' and R'' is the same or different and represents hydrogen, C₁₋₆ alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C₁₋₆ alkyl)- or heteroaryl-(C₁₋₆ alkyl)-, provided that (a) when R^{6/} is aryl it is not unsubstituted naphthyl, unsubstituted phenyl, mono-halophenyl,

5 4-methylphenyl, 4-methoxyphenyl, 4-hydroxyphenyl, 4-trifluoromethylphenyl, 4-nitrophenyl, 4-cyanophenyl, 4-n-propylphenyl, 4-t-butylphenyl, 4-n-pentylphenyl, 4-dimethylaminophenyl, 4-methylthiophenyl, 3-trifluoromethylthiophenyl, 3,4-dimethoxyphenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl or 2,3,4,5,6-pentafluorophenyl, (b) when R^{6/} is heteroaryl it is not 2-pyrrolyl, 2-pyrazinyl,

10 2-quinaldyl, 2-methyl-indolyl, 2-benzofuranyl, 2-benzothienyl, 3-thienyl, 3-indolyl, unsubstituted 2-indolyl, 5-fluoroindol-2-yl, 5-chloroindol-2-yl, 5-bromoindol-2-yl, 5-hydroxyindol-2-yl or 5-methoxyindol-2-yl, (c) when R^{6/} is aryl-(C₁₋₆ alkyl)- it is not 4-thianaphthene-(CH₂)-, (d) when R^{6/} is heteroaryl-(C₁₋₆ alkyl)- it is not -indolyl-(CH₂)_x-, wherein x is 1, 2, 3, and (e) when R' is hydrogen, R'' is not

15 4-halophenyl, 3-methylphenyl, 3-cyanophenyl, 3-aminophenyl, 3-aminocarbonylphenyl, 3-benzoic acid, 3-benzoic acid ethyl ester, 6-amino-3-pyridyl, 5-(2-chloro)pyridyl, 5-(2-methoxy)pyridyl, 5-indanyl or benzotriazol-3-yl; R^{6//} represents C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C₁₋₆ alkyl)-, heteroaryl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆ alkyl)-, heterocyclyl-(C₁₋₆ alkyl)- or -NR'R'' wherein each R' and R'' is the same or different and represents hydrogen, C₁₋₆ alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C₁₋₆ alkyl)- or heteroaryl-(C₁₋₆ alkyl)-; and

20 R^{6//} represents C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C₁₋₆ alkyl)-, heteroaryl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆ alkyl)-, heterocyclyl-(C₁₋₆ alkyl)- or -NR'R'' wherein each R' and R'' is the same or different and represents hydrogen, C₁₋₆ alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C₁₋₆ alkyl)- or heteroaryl-(C₁₋₆ alkyl)-, provided that when R^{6//} is aryl it is not 4-methylphenyl.

Preferred R¹, R², R³ and R⁴ groups in the formula (Ib) include those preferred groups set out above as preferred R¹, R², R³ and R⁴ groups in the formula (I). Preferred compounds of formula (Ib) include the particularly preferred compounds of formula (I) named above.

Typically, in the formula (Ib), R² is hydrogen.

Preferred compounds of formula (Ib) are those in which:

- R^{5/} represents C₃₋₆ alkyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C₁₋₆ alkyl)-, heteroaryl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆ alkyl)-, heterocyclyl-(C₁₋₆ alkyl)-, -
- 5 aryl-C(O)-C(O)-, heteroaryl-C(O)-C(O)-, carbocyclyl-C(O)-C(O)-, heterocyclyl-C(O)-C(O)- or -X', provided that when R^{5/} is heteroaryl it is not quinaldyl or pyrazinyl, when R^{5/} is heteroaryl-(C₁₋₆ alkyl)- it is not indolyl-(CH₂)_x-, wherein x is 1 or 2, or furanylmethyl, when R^{5/} is aryl it is not phenyl and when R^{5/} is aryl-(C₁₋₆ alkyl)- it is not phenyl-(C₁₋₃ alkyl)-;
- 10 - X' represents -CO-R^{6/}, -S(O)-R^{6//} or -S(O)₂-R^{6//};
- R^{6/} represents C₁ alkyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C₁₋₆ alkyl)-, heteroaryl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆ alkyl)-, heterocyclyl-(C₁₋₆ alkyl)-, aryl-(C₁₋₆ hydroxyalkyl)-, heteroaryl-(C₁₋₆ hydroxyalkyl)-, carbocyclyl-(C₁₋₆ hydroxyalkyl)-, heterocyclyl-(C₁₋₆ hydroxyalkyl)-,
- 15 aryl-(C₁₋₆ alkyl)-O-, heteroaryl-(C₁₋₆ alkyl)-O-, carbocyclyl-(C₁₋₆ alkyl)-O-, heterocyclyl-(C₁₋₆ alkyl)-O- or -NR'R'' wherein each R' and R'' is the same or different and represents hydrogen, C₁₋₆ alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C₁₋₆ alkyl)-, heteroaryl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆ alkyl)- or heterocyclyl-(C₁₋₆ alkyl)- provided that (a) when R^{6/} is aryl it is not phenyl or
- 20 naphthyl, (b) when R^{6/} is heteroaryl it is not thienyl, pyrrolyl, pyrazinyl, quinaldyl, quinazolidinyl, indolyl, benzofuranyl or benzothienyl, (c) when R^{6/} is aryl-(C₁₋₆ alkyl)- it is not thianaphthene-(CH₂)- or phenyl-(CH₂)₁₋₃-, (d) when R^{6/} is heteroaryl-(C₁₋₆ alkyl)- it is not indolyl-(CH₂)_x-, wherein x is 1, 2 or 3, thienyl-(CH₂)₃- or furanyl-(CH₂)₂-, (e) when R^{6/} is carbocyclyl it is not cyclohexyl, -, (f) when R^{6/} is
- 25 heterocyclyl it is not pyrrolidinyl or dihydrobenzofuranyl, (g) when R^{6/} is carbocyclyl-(C₁₋₆ alkyl)- it is not cyclohexyl-(C₁₋₃ alkyl)-, (h) when R^{6/} is aryl-(C₁₋₆ alkyl)-O- it is not phenyl-(CH₂)-O- and (i) when R' is hydrogen, R'' is not phenyl, pyridyl, indanyl, C₄ alkyl, cyclohenyl, naphthyl, phenyl-CH₂-, benzotriazolyl and when R' is methyl, R'' is not cyclopropylbenzene;
- 30 - R^{6//} represents C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C₁₋₆ alkyl)-, heteroaryl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆ alkyl)-, heterocyclyl-(C₁₋₆ alkyl)-, aryl-(C₁₋₆ hydroxyalkyl)-, heteroaryl-(C₁₋₆

hydroxyalkyl)-, carbocyclyl-(C₁₋₆ hydroxyalkyl)-, heterocyclyl-(C₁₋₆ hydroxyalkyl)-, aryl-(C₁₋₆ alkyl)-O-, heteroaryl-(C₁₋₆ alkyl)-O-, carbocyclyl-(C₁₋₆ alkyl)-O-, heterocyclyl-(C₁₋₆ alkyl)-O- or -NR'R'' wherein each R' and R'' is the same or different and represents hydrogen, C₁₋₆ alkyl, carbocyclyl, heterocyclyl, aryl, 5 heteroaryl, aryl-(C₁₋₆ alkyl)-, heteroaryl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆ alkyl)- or heterocyclyl-(C₁₋₆ alkyl)-; and

- R^{6//} represents C₁₋₁₈ alkyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C₁₋₆ alkyl)-, heteroaryl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆ alkyl)-, heterocyclyl-(C₁₋₆ alkyl)-, aryl-(C₁₋₆ hydroxyalkyl)-, 10 heteroaryl-(C₁₋₆ hydroxyalkyl)-, carbocyclyl-(C₁₋₆ hydroxyalkyl)-, heterocyclyl-(C₁₋₆ hydroxyalkyl)-, aryl-(C₁₋₆ alkyl)-O-, heteroaryl-(C₁₋₆ alkyl)-O-, carbocyclyl-(C₁₋₆ alkyl)-O-, heterocyclyl-(C₁₋₆ alkyl)-O- or -NR'R'' wherein each R' and R'' is the same or different and represents hydrogen, C₁₋₆ alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C₁₋₆ alkyl)-, heteroaryl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆ alkyl)- or 15 heterocyclyl-(C₁₋₆ alkyl)-, provided that when R^{6//} is aryl it is not methylphenyl.

Examples of preferred compounds of formula (Ib) are compounds defined above as preferred compounds of formula (Ib) wherein:

- R^{5/} represents C₂₋₆ alkyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C₁₋₆ alkyl)-, heteroaryl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆ alkyl)-, heterocyclyl-(C₁₋₆ alkyl)- or 20 -X', provided that when R^{5/} is heteroaryl it is not quinaldyl or pyrazinyl and when R^{5/} is heteroaryl-(C₁₋₆ alkyl)- it is not indolyl-(CH₂)_x-, wherein x is 1 or 2.;
- R^{6/} represents C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C₁₋₆ alkyl)-, heteroaryl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆ alkyl)-, heterocyclyl-(C₁₋₆ alkyl)- or -NR'R'' wherein each R' and R'' is the same or 25 different and represents hydrogen, C₁₋₆ alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C₁₋₆ alkyl)- or heteroaryl-(C₁₋₆ alkyl)-, provided that (a) when R^{6/} is aryl it is not phenyl or naphthyl, (b) when R^{6/} is heteroaryl it is not thienyl, pyrrolyl, pyrazinyl, quinaldyl, indolyl, benzofuranyl or benzothienyl, (c) when R^{6/} is aryl-(C₁₋₆ alkyl)- it is not thianaphthene-(CH₂)-, (d) , when R^{6/} is heteroaryl-(C₁₋₆ alkyl)- it is 30 not indolyl-(CH₂)_x-, wherein x is 1, 2, 3, and (e) when R' is hydrogen, R'' is not phenyl, pyridyl, indanyl or benzotriazolyl;
- R^{6//} represents C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, aryl, heteroaryl,

carbocyclyl, heterocyclyl, aryl-(C₁₋₆ alkyl)-, heteroaryl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆ alkyl)-, heterocyclyl-(C₁₋₆ alkyl)- or -NR'R'' wherein each R' and R'' is the same or different and represents hydrogen, C₁₋₆ alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C₁₋₆ alkyl)- or heteroaryl-(C₁₋₆ alkyl)-; and

5 - R^{6//} represents C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C₁₋₆ alkyl)-, heteroaryl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆ alkyl)-, heterocyclyl-(C₁₋₆ alkyl)- or -NR'R'' wherein each R' and R'' is the same or different and represents hydrogen, C₁₋₆ alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C₁₋₆ alkyl)- or heteroaryl-(C₁₋₆ alkyl)-, provided that when R^{6//} is aryl it is not methylphenyl.

Further preferred compounds of formula (Ib) are those wherein:

- R^{5/} is C₃₋₆ alkyl, C₃₋₆ cycloalkyl, heterocyclyl, C₃₋₆ cycloalkyl-(C₁₋₆ alkyl), aryl-C(O)-C(O)-, heteroaryl-C(O)-C(O)-, carbocyclyl-C(O)-C(O)-, heterocyclyl-C(O)-C(O)- or -X';
- 15 - X' is -CO-R^{6/}, -S(O)-R^{6//} or -S(O)₂-R^{6//};
- R^{6/} is C₁ alkyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, heterocyclyl-(C₁₋₆ alkyl)-, aryl-(C₁₋₆ hydroxyalkyl)-, heteroaryl-(C₁₋₆ hydroxyalkyl)-, carbocyclyl-(C₁₋₆ hydroxyalkyl)-, heterocyclyl-(C₁₋₆ hydroxyalkyl)-, heteroaryl-(C₁₋₆ alkyl)-O-, carbocyclyl-(C₁₋₆ alkyl)-O-, heterocyclyl-(C₁₋₆ alkyl)-O- or -NR'R'' wherein each R' and R'' is the same or different and represents hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, heterocyclyl, carbocyclyl-(C₁₋₆ alkyl)- or heterocyclyl-(C₁₋₆ alkyl)-;
- R^{6//} represents C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C₁₋₆ alkyl)-, heteroaryl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆ alkyl)-, heterocyclyl-(C₁₋₆ alkyl)-, aryl-(C₁₋₆ hydroxyalkyl)-, heteroaryl-(C₁₋₆ hydroxyalkyl)-, carbocyclyl-(C₁₋₆ hydroxyalkyl)-, heterocyclyl-(C₁₋₆ hydroxyalkyl)-, heteroaryl-(C₁₋₆ alkyl)-O-, heteroaryl-(C₁₋₆ alkyl)-O-, carbocyclyl-(C₁₋₆ alkyl)-O-, heterocyclyl-(C₁₋₆ alkyl)-O- or -NR'R'' wherein each R' and R'' is the same or different and represents hydrogen, C₁₋₃ alkyl, heterocyclyl, heteroaryl, heteroaryl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆ alkyl)- or heterocyclyl-(C₁₋₆ alkyl)-; and
- 25 - R^{6//} is C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₃₋₆ cycloalkyl, heterocyclyl, C₃₋₆ cycloalkyl-(C₁₋₆ alkyl)-, heterocyclyl-(C₁₋₆ alkyl)-, aryl-(C₁₋₆ hydroxyalkyl)-, heteroaryl-(C₁₋₆ hydroxyalkyl)-, carbocyclyl-(C₁₋₆ hydroxyalkyl)-,
- 30 - R^{6//} is C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₃₋₆ cycloalkyl, heterocyclyl, C₃₋₆ cycloalkyl-(C₁₋₆ alkyl)-, heterocyclyl-(C₁₋₆ alkyl)-, aryl-(C₁₋₆ hydroxyalkyl)-, heteroaryl-(C₁₋₆ hydroxyalkyl)-, carbocyclyl-(C₁₋₆ hydroxyalkyl)-,

heterocyclyl-(C₁₋₆ hydroxyalkyl)-, aryl-(C₁₋₆ alkyl)-O-, heteroaryl-(C₁₋₆ alkyl)-O-, carbocyclyl-(C₁₋₆ alkyl)-O-, heterocyclyl-(C₁₋₆ alkyl)-O- or -NR'R'' wherein each R' and R'' is the same or different and represents hydrogen, C₁₋₆ alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C₁₋₆ alkyl)-, heteroaryl-(C₁₋₆ alkyl), carbocyclyl-(C₁₋₆ alkyl)- or heterocyclyl-(C₁₋₆ alkyl)-.

5 Examples of further preferred compounds of formula (Ib) are compounds as defined as further preferred compounds of formula (Ib) wherein:

- R^{5/} is C₂₋₆ alkyl, C₃₋₆ cycloalkyl, heterocyclyl, C₃₋₆ cycloalkyl-(C₁₋₆ alkyl), heterocyclyl-(C₁₋₆ alkyl) or -X';
- 10 - X' is -CO-R^{6/}, -S(O)-R^{6//} or -S(O)₂-R^{6//};
- R^{6/} is C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₃₋₆ cycloalkyl, heterocyclyl, C₃₋₆ cycloalkyl-(C₁₋₆ alkyl)-, heterocyclyl-(C₁₋₆ alkyl)- or -NR'R'' wherein each R' and R'' is the same or different and represents hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl or heterocyclyl;
- 15 - R^{6//} represents C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C₁₋₆ alkyl)-, heteroaryl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆ alkyl)-, heterocyclyl-(C₁₋₆ alkyl)- or -NR'R'' wherein each R' and R'' is the same or different and represents hydrogen, C₁₋₆ alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C₁₋₆ alkyl)- or heteroaryl-(C₁₋₆ alkyl)-; and
- 20 - R^{6///} is C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₃₋₆ cycloalkyl, heterocyclyl, C₃₋₆ cycloalkyl-(C₁₋₆ alkyl)-, heterocyclyl-(C₁₋₆ alkyl)- or -NR'R'' wherein each R' and R'' is the same or different and represents hydrogen, C₁₋₆ alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C₁₋₆ alkyl)- or heteroaryl-(C₁₋₆ alkyl)-.

25 Preferably, in said further preferred compounds of formula (Ib), the cycloalkyl, heterocyclyl and carbocyclyl moieties in the groups R^{5/}, R^{6/}, R^{6//} and R^{6///} are unsubstituted or substituted by 1, 2 or 3 substituents selected from halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, nitro and cyano,

30 More preferably, in said further preferred compounds of formula (Ib), the cycloalkyl, heterocyclyl, carbocyclyl, aryl and heteroaryl moieties in the groups R' and R'' are unsubstituted or substituted by 1, 2 or 3 substituents selected from

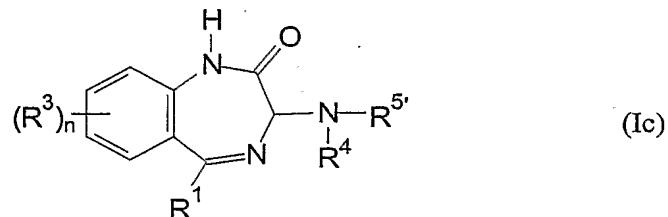
halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, nitro and cyano.

Preferably, in said further preferred compounds of formula (Ib), the cycloalkyl, heterocyclyl and carbocyclyl moieties in the groups R^{5/}, R^{6/}, R^{6//} and R^{6///} 5 are unsubstituted or substituted by 1, 2 or 3 substituents selected from halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, nitro and cyano,

More preferably, in said further preferred compounds of formula (Ib), the cycloalkyl, heterocyclyl, carbocyclyl, aryl and heteroaryl moieties in the groups 10 R^{5/} and R^{6//} are unsubstituted or substituted by 1, 2 or 3 substituents selected from halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, nitro and cyano.

Particularly preferred novel compounds of the invention are compounds of formula (Ic) are pharmaceutically acceptable salts thereof

15



wherein:

- R¹ is phenyl or methyl;
- 20 - R³ is methyl or chlorine;
- n is 0 or 1;
- R⁴ is hydrogen or methyl;
- R^{5'} is phenyl-CH₂- thienyl-C(O)-C(O)- or -X';
- X' is -CO-R^{6'}, -CONR'R'', -S(O)₂R^{6'''} or -S(O)₂-NR/R//; and
- 25 - R^{6'} is C₁ alkyl, C₁₋₄ alkoxy, benzodioxinyl, 9H-fluoren-9-onyl, furanyl, oxazolyl, isoxazolyl, pyrazolyl, pyridyl, cyclopentyl, piperazinyl, piperidinyl, morpholinyl, phenyl-CH₂-CH(OH)-, phenyl-CH(OH)-CH₂-, phenyl-(C₂ alkyl)-O- or 1H-benzo[d]imidazol-2(3H)-only;

- $R^{6''}$ is C_{1-4} alkyl, C_{1-4} alkoxy, phenyl, naphthyl, dihydrobenzofuranyl, benzodioxinyl, 9H-fluoren-9-onyl, indolyl, thienyl, furanyl, oxazolyl, isoxazolyl, pyrazolyl, pyridyl, benzothienyl, benzofuranyl, cyclopentyl, cyclohexyl, piperazinyl, piperidinyl, morpholinyl, phenyl-(C_{1-2} alkyl)-, phenyl- $CH_2-CH(OH)-$, phenyl- $CH(OH)-CH_2-$, phenyl-(C_{1-2} alkyl)-O- or 1*H*-benzo[*d*]imidazol-2(3*H*)-only;
- each R' and R'' is the same or different and represents hydrogen, C_{1-4} alkyl, phenyl, thienyl, cyclohexyl, cyclopentyl or phenyl-(CH_2)-; and
- each R_1 and R_2 is the same or different and represents hydrogen, C_{1-4} alkyl, phenyl, thienyl, cyclohexyl, cyclopentyl or phenyl-(CH_2)-, wherein:

10 the phenyl moiety in the group R^1 being unsubstituted or substituted by a single fluorine, chlorine, C_{1-2} alkyl, C_{1-2} alkoxy, C_{1-2} alkylthio, C_{1-2} haloalkyl or C_{1-2} haloalkoxy substituent;

the aryl moieties in the groups $R^{5'}$, $R^{6'}$ and $R^{6''}$ being unsubstituted or substituted by 1,2 or 3 substituents selected from fluorine, chlorine, bromine, iodine, C_{1-4} alkyl, C_{2-4} acyl, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-6} haloalkyl, C_{1-4} haloalkoxy, amino, mono(C_{1-4} alkyl)amino, di(C_{1-4} alkyl)amino, nitro, $-CO_2R'$, $-S(O)_2R'$ and $-S(O)_2NH_2$, wherein R' represents C_{1-2} alkyl;

the heteroaryl moieties in the groups $R^{5'}$, $R^{6'}$ and $R^{6''}$ being unsubstituted or substituted by 1 or 2 substituents selected from fluorine, chlorine, bromine, C_{1-2} alkyl, C_{1-2} haloalkyl and di(C_{1-2} alkyl)amino;

the heterocyclyl and carbocyclyl moieties in the $R^{6''}$ group being unsubstituted or substituted by 1 or 2 substituents selected from fluorine, chlorine, bromine, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl and nitro;

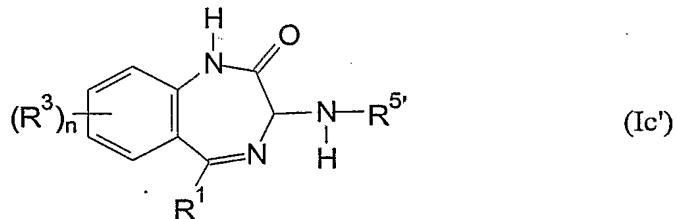
the aryl, heteroaryl and carbocyclyl moieties in the R' and R'' being unsubstituted or substituted by one or two substituents selected from fluorine, chlorine, bromine, C_{1-2} alkyl, C_{1-2} alkoxy, C_{1-2} alkylthio, C_{1-2} haloalkyl and nitro; and

the aryl, heteroaryl and carbocyclyl moieties in the R_1 and R_2 being unsubstituted or substituted by one or two substituents selected from fluorine, chlorine, bromine, C_{1-2} alkyl, C_{1-2} alkoxy, C_{1-2} alkylthio, C_{1-2} haloalkyl and nitro,

20 provided that the compound of formula (Ic) is not N-(2-Oxo-5-phenyl-2,3-dihydro-1*H*-benzo[e][1,4]diazepin-3-yl)-acetamide.

Examples of particularly preferred novel compounds of the present

invention are compounds of formula (Ic') and pharmaceutically acceptable salts thereof



wherein:

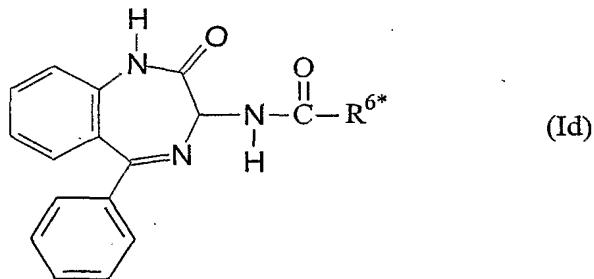
- 5 - R¹ is phenyl or methyl;
- R³ is chlorine;
- n is 0 or 1;
- R^{5'} is phenyl-CH₂-, furanyl-CH₂- or -X';
- X' is -CO-R^{6'}, -CO-NR'⁷R⁸, -S(O)₂-R^{6'''} or -S(O)₂-NR₉R₁₀;
- 10 - R^{6'} is C₁₋₄ alkyl, 2-thienyl, furanyl, pyridyl, cyclopentyl, cyclohexyl, 3-benzothienyl, dihydrobenzofuranyl, isoxazolyl, piperidinyl, for example N-piperidinyl, morpholinyl, for example N-morpholinyl, piperazinyl, for example N-piperazinyl;
- R^{6'''} is C₁₋₄ alkyl, phenyl, thienyl, furanyl, pyridyl, cyclopentyl, cyclohexyl, benzothienyl, dihydrobenzofuranyl, isoxazolyl, piperidinyl, for example N-piperidinyl, morpholinyl, for example N-morpholinyl or piperazinyl, for example N-piperazinyl;
- 15 - each R'⁷ and R⁸ is the same or different and represents hydrogen, C₁₋₄ alkyl, cyclohexyl, cyclopentyl, phenyl or phenyl-CH₂-; and
- 20 - each R₉ and R₁₀ is the same or different and represents hydrogen, C₁₋₄ alkyl, cyclohexyl, cyclopentyl, phenyl or phenyl-CH₂-
the phenyl, thienyl, furanyl, pyridyl, cyclopentyl, cyclohexyl, benzothienyl, dihydrobenzofuranyl, isoxazolyl, piperidinyl, morpholinyl and piperazinyl moieties in the groups R⁵ and R^{6'} being unsubstituted or substituted by 1 or 2 substituents
- 25 - selected from fluorine, chlorine, bromine, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl and nitro,
the thienyl, furanyl, pyridyl, cyclopentyl, cyclohexyl, benzothienyl, dihydrobenzofuranyl, isoxazolyl, piperidinyl, morpholinyl and piperazinyl moieties

in the group $R^{6//}$ being unsubstituted or substituted by 1 or 2 substituents selected from fluorine, chlorine, bromine, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl and nitro,
 the phenyl moiety in the group $R^{6//}$ being unsubstituted or substituted by 1 or 2 substituents selected from fluorine, chlorine, bromine, C_{2-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl and nitro,
 5 the cyclohexyl and cyclopentyl moieties in the groups R' and R'' being unsubstituted or substituted by a single fluoro, chloro, methyl, methoxy or nitro substituent,
 the phenyl moiety in the groups R' and R'' being unsubstituted or substituted
 10 by a single methoxy or nitro substituent, and
 the phenyl, cyclohexyl and cyclopentyl moieties in the groups R_1 and $R_{1//}$ being unsubstituted or substituted by a single fluoro, chloro, methyl, methoxy or nitro substituent.

Further preferred novel compounds of the present invention are
 15 compounds of formula (Ic), and pharmaceutically acceptable salts thereof, where:
 - $R^{5/}$ is $-X'$;
 - X' is $-CO-R^{6/}$, $-CO-NR' R''$, $-S(O)_2-R^{6//}$ or $-S(O)_2-NR R_{1//}$;
 - $R^{6/}$ is C_{1-4} alkyl, pyridyl, cyclopentyl, cyclohexyl, dihydrobenzofuranyl, isoxazolyl, piperidinyl, for example N-piperidinyl, morpholinyl, for example N-
 20 morpholinyl, piperazinyl, for example N-piperazinyl;
 - $R^{6//}$ is C_{1-4} alkyl, pyridyl, cyclopentyl, cyclohexyl, dihydrobenzofuranyl, isoxazolyl, piperidinyl, for example N-piperidinyl, morpholinyl, for example N-morpholinyl, piperazinyl, for example N-piperazinyl;
 - each R' and R'' is the same or different and represents hydrogen, C_{1-4} alkyl, cyclohexyl or cyclopentyl; and
 25 - each R_1 and $R_{1//}$ is the same or different and represents hydrogen, C_{1-4} alkyl, cyclohexyl, cyclopentyl, phenyl or phenyl- CH_2- ,
 the pyridyl, cyclopentyl, cyclohexyl, dihydrobenzofuranyl, isoxazolyl, piperidinyl, morpholinyl, piperazinyl moieties in the groups $R^{6/}$ and $R^{6//}$ being
 30 unsubstituted or substituted by 1 or 2 substituents selected from fluorine, chlorine, bromine, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl and nitro, and

the phenyl, cyclohexyl and cyclopentyl moieties in the groups R', R'', R₁ and R₂ being unsubstituted or substituted by a single fluoro, chloro, methyl, methoxy or nitro substituent.

Further preferred novel compounds of the present invention are compounds 5 of formula (Id) and pharmaceutically acceptable salts thereof



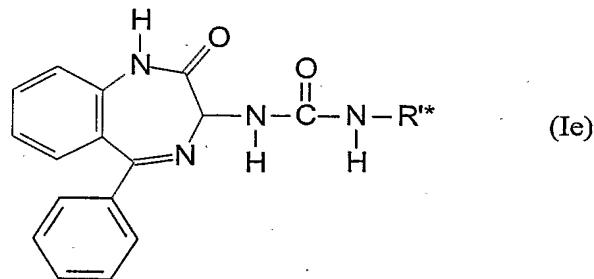
wherein R^{6*} is an aryl group which is unsubstituted or substituted by 1, 2 or 3 substituents selected from halogen, C₁₋₆ alkyl, C₂₋₇ acyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, nitro, cyano, carbamoyl, mono(C₁₋₆ alkyl)carbamoyl, di(C₁₋₆ alkyl)carbamoyl, amino, mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, -CO₂R', -CONR'R'', -S(O)R', -S(O)₂R', -S(O)NR'R'', -S(O)₂NR'R'', -NH-S(O)₂R' or -NH-CO-R', wherein each R' and R'' is the same or different and 15 represents hydrogen or C₁₋₆ alkyl, provided that R^{6*} is not a 4-chlorophenyl group.

Typically, in the compounds of formula (Id) R^{6*} is a phenyl group which is unsubstituted or substituted by 1, 2 or 3 substituents selected from halogen, C₁₋₆ alkyl, C₂₋₇ acyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, amino, mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, nitro, cyano, -CO₂R', -S(O)R', -S(O)₂R' and -S(O)₂NR'R'', wherein each R' and R'' is the same or different and 20 represents hydrogen or C₁₋₄ alkyl, provided that R^{6*} is not a 4-haolphenyl group.

Preferably, in compounds of formual (Id), R^{6*} is a phenyl group which is unsubstituted or substituted by 1, 2 or 3 substituents selected from fluorine, chlorine, bromine, iodine, C₁₋₄ alkyl, C₂₋₄ acyl, hydroxy, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, amino, mono(C₁₋₄ alkyl)amino, di(C₁₋₄ alkyl)amino, nitro, -CO₂R', -S(O)R' and -S(O)₂NH₂, wherein R' represents C₁₋₂ alkyl, provided that R^{6*} is not a monohalophenyl group.

More preferably, in compounds of formula (Id), R^{6*} is a phenyl group which is unsubstituted or substituted by 1 or 2 substituents selected from C₁₋₂ alkyl, C₁₋₂ alkoxy, C₁₋₂ alkylthio, C₁₋₂ haloalkyl, C₁₋₂ haloalkoxy and nitro.

Further preferred novel compounds of the present invention are compounds 5 of formula (Ie) and pharmaceutically acceptable salts thereof



10 wherein R'* is an aryl group which is unsubstituted or substituted by 1 or 2 substituents selected from fluorine, chlorine, bromine, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy and nitro.

Preferably, in compounds of formula (Ie), R'* is a phenyl group which is unsubstituted or substituted by one or two substituents selected from fluorine, 15 chlorine, bromine, C₁₋₂ alkyl, C₁₋₂ alkoxy, C₁₋₂ alkylthio, C₁₋₂ haloalkyl and nitro.

More preferably, in compounds of formula (Ie), R'* is a phenyl group which is unsubstituted or substituted by a single fluorine, chlorine or bromine substituent.

The present invention also relates to the novel compounds, as defined 20 above, or a pharmaceutically acceptable salt thereof, for use in a method of treating the human or animal body. The present invention also relates to a pharmaceutical composition comprising a novel compound as defined above and a pharmaceutically acceptable diluent or carrier. Preferably, the pharmaceutical composition comprises a pharmaceutically acceptable salt of a novel compound as defined above. A 25 pharmaceutically acceptable salt is as defined above. The novel compounds of the invention are typically administered in the manner defined above and the compounds are typically formulated for administration in the manner defined above.

Preferably, the pharmaceutical compositions comprise optically active isomers of the novel compounds of the invention. Thus, for example, preferred novel compounds of the invention containing only one chiral centre include an R enantiomer in substantially pure form, an S enantiomer in substantially pure form and enantiomeric mixtures which contain an excess of the R enantiomer or an excess of the S enantiomer. It is particularly preferred that pharmaceutical contains a compound of the invention which is a substantially pure optical isomer. For the avoidance of doubt, the novel compounds of the invention can, if desired, be used in the form of solvates.

10

The following Examples illustrate the invention. They do not however, limit the invention in any way. In this regard, it is important to understand that the particular assays used in the Examples section are designed only to provide an indication of anti-RSV activity. There are many assays available to determine the activity of given compounds against RSV, and a negative result in any one particular assay is therefore not determinative.

EXAMPLES

In this section, all temperatures are in °C. Flash column chromatography was carried out using Merck 9385 silica. Solid phase extraction (SPE) chromatography was 5 carried out using Jones Chromatography (Si) cartridges under 15mmHg vacuum with stepped gradient elution. Thin layer chromatography (TLC) was carried out on plastic plates.

LC-MS CONDITIONS

10 Samples were run on a MicroMass ZMD, using electrospray with simultaneous positive – negative ion detection.
Column : YMC-PACK FL-ODS AQ, 50 x 4.6mm I.D S-5μm.
Gradient : 95:5 to 5:95 v/v H₂O/CH₃CN + 0.05% Formic Acid over 4.0 min, hold 3 min, return to 95:5 v/v H₂O/CH₃CN + 0.05% Formic Acid over 0.2 min and hold at 15 95:5 v/v H₂O/CH₃CN + 0.05% Formic Acid over 3 min.
Detection : PDA 250 – 340 nm.
Flow rate : 1.5 ml/min

Preparation Intermediate 1

20 Benzotriazol-1-yl-benzyloxycarbonylamino-acetic acid
A mixture of glyoxylic acid monohydrate (4.60g), benzotriazole (5.95g) and benzyl carbamate (7.55g) was heated to reflux in toluene (100ml) for 18h, under Dean-Stark 25 conditions. The mixture was then allowed to cool to room temperature, and the resulting precipitate collected by filtration. This was then recrystallised from diethyl ether giving an off-white solid (11.66g)

30 ¹H NMR (d6 DMSO, δ) 5.07 (q+s, 3H) 7.25 (d, 1H) 7.3-7.63 (m,6H) 7.92-8.10 (m, 2H) 9.32 (d, 1H)
LC/MS Found ES- = 325 RT= 4.68min

Preparation Intermediate 2

(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-carbamic acid benzyl ester

5

A cold (0°C) solution of Intermediate 1 (11.6g) in dry THF (100ml) under nitrogen was stirred, and was treated dropwise with a solution of oxalyl chloride (4.4g) in dry dichloromethane (50ml), followed by dry dimethylformamide (2ml). This resulting mixture was stirred for 2h, and was then treated with a solution of 2-(amino-phenyl)-phenyl-methanone (6.1g) and N-methylmorpholine (7.07g) in dry THF (50ml) over 30 minutes. The reaction mixture was then allowed to warm to room temperature and was then filtered to remove inorganic salts. The mother liquors were then treated with 7M ammonia in methanol (100ml) and stirring continued for 18h. The solvents were then evaporated and the residue partitioned between ethyl acetate and 1M sodium hydroxide. The dried extracts were evaporated, and the crude oil dissolved in acetic acid (200ml) containing ammonium acetate (13.4g). This mixture was then stirred at room temperature for 18h. The solvents were then evaporated and the residue was suspended in ethyl acetate:diethyl ether (1:3) (200ml). 1M sodium hydroxide was added until pH8 was reached, and then the mixture was cooled to 0-5°C and the resulting solid collected by filtration (6.94g)

¹H NMR (d6 DMSO, δ) 5.05 (s, 1H) 5.09 (m, 2H) 7.25-7.69 (m, 14H) 8.38 (d, 1H) 10.85 (s, 1H)

LC/MS Found ES+= 386 RT= 5.46min

25

Preparation Intermediate 3

3-Amino-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

30 Intermediate 2 (1.07g) was dissolved in 48% hydrobromic acid in acetic acid (30ml) and was heated to 70°C for 30mins. The mixture was then allowed to cool, and was diluted with diethyl ether (30ml). This led to the formation of a yellow solid which

was collected by filtration. This material was then partitioned between ethyl acetate and 1M potassium carbonate solution. The extracts were dried, and then evaporated giving an oil which was triturated with diethyl ether giving an off-white solid (0.35g)
¹H NMR (d6 DMSO, δ) 4.25 (s, 1H) 7.17-7.66 (m, 9H) 10.65 (brs, 1H)
5 LC/MS RT= 3.23min, but with no associated molecular ion.

Preparation Intermediate 4

10 [Benzotriazol-1-yl(2-benzoyl-4-chloro-phenylcarbamoyl)-methyl]-carbamic acid
benzyl ester

The acid chloride of Intermediate 1 was prepared as previously described from 5g of Intermediate 1. This was added to a stirred solution of (2-amino-5-chloro-phenyl)-phenyl-methanone (3.48g) and N-methylmorpholine (3.1g) in THF (40ml) at 0°C.
15 After addition the mixture was allowed to warm to room temperature, and was stirred for 1h. The precipitate was removed by filtration, and the solvent evaporated giving a gummy solid, which was used without purification or characterisation.

Preparation Intermediate 5

20 (7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-carbamic acid benzyl ester

A solution of Intermediate 4 in 7M ammonia in methanol (100ml) was stirred at
25 room temperature for 5h. The solvent was evaporated, and the residue partitioned between ethyl acetate, and 1M sodium hydroxide. The dried organic layer was evaporated, and the residue dissolved in acetic acid (200ml) containing ammonium acetate (5.8g). The resulting mixture was stirred at room temperature for 18h, and then the solvent was evaporated. The residue was dissolved in water and ethyl
30 acetate, and the pH was adjusted to ca.8 with sodium hydroxide. The dried organic extracts were evaporated, and the residue triturated with diethyl ether giving a beige solid (3.27g).

LC/MS Found ES⁺ = 420,422 (C₂₃H₁₃ClN₃O₃ = 419.5)

Preparation Intermediate 6

5 3-Amino-7-chloro-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

A solution of Intermediate 5 (3.25g) in 45% hydrogen bromide in acetic acid (85ml) was heated to 70°C for 2h. The mixture was then allowed to cool, and was diluted with diethyl ether. The hydrobromide salt of the title compound was obtained by 10 filtration and dried, giving a bright yellow solid (2.7g)

NMR (δ , d6 DMSO) 5.18 (d, 1H) 7.32 (d, 1H) 7.40 (d, 1H) 7.47-7.53 (m, 5H) 7.77 (dd, 1H) 9.07 (brs, 2H) 11.41 (s, 1H)

15 Preparation Intermediate 7

[(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-ylcarbamoyl)-phenyl-methyl]-carbamic acid tert-butyl ester.

20 A solution of Intermediate 3 (34.9g), (S)-2-tert-Butoxycarbonylamino-3-phenyl-propionic acid (55.3g), triethylamine (100ml) and O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (116g) in dichloromethane (1000ml) was stirred at room temperature for 18h. under nitrogen. The solvent was then evaporated and the residue partitioned between 10% citric acid solution and ethyl acetate. The 25 organic phase was further washed with 2M sodium hydroxide, water and brine before being dried (MgSO₄). The organic phase was evaporated giving an oil which was used crude in the following step.

LC/MS RT = 5.98 min, Found ES⁺ = 498

30 ¹H NMR (DMSO, δ) 1.29 (s, 9H) 2.72-2.84 (m, 1H), 3.05-3.18 (m, 1H), 4.32-4.44 (m, 1H), 5.20-5.25 (m, 1H), 6.97-7.05 (m, 1H), 7.16-7.68 (m, 14H), 9.17-9.21 (d, 1H), 10.90 (s, 1H).

Preparation Intermediate 8

5 2-Amino-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-phenyl-acetamide.

Intermediate 7 (81.94 g) was added in a single portion to a cooled (-10 °C) solution of HCl (34 g) in ethyl acetate (1 L). The reaction was stirred at this temperature for 1 hour, before being warmed to 20 °C and stirred for a further 2 hours. The reaction was then cooled to 0 °C and water (300 mL) added at a rate that maintained a temperature below 10 °C. The aqueous layer was then washed with ethyl acetate (2 x 150 mL) and the aqueous layer returned to the reaction flask. The reaction was again cooled to 0 °C and concentrated aqueous ammonia added at a rate that maintained the temperature below 5 °C until pH 9.0 had been achieved. The reaction was then washed with ethyl acetate (5 x 150 mL) and the combined organic extracts washed with brine (100 mL), dried with magnesium sulphate and the solvent evaporated producing a yellow oil. The yellow oil was then stirred rapidly with a 5% solution of methanol in ethyl acetate until a thick white precipitate formed. The precipitate was filtered and the mother liquor again evaporated. The residual gum was again stirred with 5% methanol in ethyl acetate until a thick precipitate had formed. This sequence was repeated several times. On each occasion the precipitate was analysed to assess the diastereomeric excess by TLC (SiO₂, DCM:EtOH:NH₃, 200:8:1). Pure or mostly pure batches of each diastereomer were kept aside and mixtures returned to the precipitation procedure at the evaporation stage after first dissolving in a mixture of 5% methanol in dichloromethane. The combined batches that contained pure or mainly pure required diastereomer ($R_f = 0.25$, higher spot) were stirred as a slurry in 5% methanol in ethyl acetate for 10 minutes and filtered to produce the required diastereomer (>99% d.e.), pure sample as a white powder (26.1 g).

LC/MS RT = 3.83 min Found ES⁺ = 399

¹H NMR (CDCl₃, δ) 1.36 (bs, 2H), 2.72 (dd, 1H,), 3.24 (dd, 1H,), 3.63 (dd, 1H,), 5.46 (d, 1H,), 7.44-7.03 (m, 14H), 8.43 (s, 1H), 8.79 (d, 1H,).

Preparation Intermediate 9

5

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-phenyl-2-(3-phenyl-thioureido)-acetamide

10 A solution of Intermediate 8 (26.1g) in dichloromethane (500ml) was treated with isothiocyanato-benzene (14.7g) and the mixture left to stir at room temperature for 18h. The solvent and excess reagent was removed by evaporation and the residue redissolved in dichloromethane and then diluted with petrol giving a colourless solid which was collected by filtration (36.1g)

15 LC/MS Found ES⁺=532 RT= 5.47min

¹H NMR (CDCl₃, δ) 3.83-5.0 (m, 2H), 5.58-6.87 (m, 2H), 6.68 (d, 1H), 6.89-7.40 (m, 19H), 7.56 (d, 1H), 8.20 (bs, 1H), 9.52 (bs, 1H).

Preparation Intermediate 10

20

(S)-3-Amino-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

25 Intermediate 9 (24g) was heated to 50C and was then treated with trifluoroacetic acid (64ml). The mixture was stirred rapidly for 40mins and was then evaporated to dryness, giving a yellow oil. This material was purified by silica gel chromatography. Elution with dichloromethane:methanol:acetic acid:water; 90:10:1:1 gave the acetate salt of the amine as a pale yellow foam (13.1g).

LC/MS RT = 3.64 min Found ES⁺ = 252

30 ¹H NMR (CDCl₃, δ) 2.17 (s, 3H) 4.68 (brs, 1H) 6.98-7.47 (m, 9H) 9.56 (brs, 1H) 10.68 (brs, 1H)

The free base of this material may be isolated as follows. 0.5g of this material was dissolved in dichloromethane (1ml) and was basified by the addition of 0.880 ammonia (1ml) giving a colourless precipitate which was collected by filtration and dried (380mg)

5

Example 1

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-acetamide

10 A solution of Intermediate 3 (300mg) in pyridine (5ml) was treated with acetic anhydride (183mg). The mixture was stirred at room temperature for 1.5h and was then evaporated. The residue was partitioned between water and dichloromethane. The dried extract was evaporated and the residue triturated with petroleum ether giving a colourless solid (231mg)

15

LC/MS RT=3.82 min Found ES- = 292

¹H NMR (δ , d₆ DMSO) 1.99 (s, 3H) 5.25 (d, 1H) 7.21-7.66 (m, 9H) 9.06 (s, 1H) 10.81 (s, 1H)

20 Example 2

1,1-Diethyl-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea

25 A solution of Intermediate 3 (100mg) in dichloromethane:dimethylformamide (9:1; 2ml) containing diisopropylethylamine (62mg) was treated with diethylcarbamoyl chloride (0.05ml). The resulting mixture was stirred under nitrogen at room temperature for 18h, and was then partitioned between water and dichloromethane. The organic extract was evaporated and the residue was purified on a silica gel SPE cartridge. Elution with 10% methanol in ethyl acetate gave a colourless solid (34mg).

30

LC/MS RT=4.37 min Found ES+ = 351

¹H NMR (d₆ DMSO, δ) 1.11 (t,6H) 2.50 (br,4H) 5.20 (d,1H) 6.83 (d,1H) 7.20-7.66

(m,9H) 10.78 (brs,1H)

Example 3

5 N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-propionamide

This material was prepared as described for Example 2 except that propionyl chloride (0.035ml) was used. The title compound was a colourless solid (11mg)

10 LC/MS RT= 4.03min Found ES+ =308

¹H NMR (d6 DMSO, δ) 1.03 (t,3H) 2.31 (q,2H) 5.26 (d,1H) 7.20-7.67 (m,9H) 8.94 (d,1H) 10.80 (s,1H)

Example 4

15

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-butyramide

This material was prepared as described for Example 2 except that butyryl chloride (0.041ml) was used. The title compound was a colourless solid (31mg)

20 LC/MS RT= 4.31min Found ES+ =320

¹H NMR (d6 DMSO, δ) 0.90 (brt,3H) 1.55 (br,2H) 2.27 (brq,2H) 5.26 (brd,1H) 7.20-7.70 (m,9H) 8.95 (brd,1H) 10.80 (s,1H)

Example 5

25

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-isobutyramide

This material was prepared as described for Example 2 except that isobutyryl chloride (41ml) was used. The title compound was a colourless solid (35mg)

30 LC/MS RT= 4.30min Found ES+ =322

¹H NMR (d6 DMSO, δ) 1.03 (d,6H) 2.72 (septet,1H) 5.23 (d,1H) 7.20-7.68 (m,9H)

8.90 (d,1H) 10.77 (brs,1H)

Example 6

5 2,2-Dimethyl-N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-propionamide

This material was prepared as described for Example 2 except that 2,2-dimethylpropionyl chloride (0.049ml) was used. The title compound was a colourless
10 solid (22mg)

LC/MS RT= 4.74min Found ES+ =336

¹H NMR (d6 DMSO, δ) 1.20 (s,9H) 5.23 (d,1H) 7.20-7.68 (m,9H) 8.22 (d,1H) 10.80
(br,1H)

15

Example 7

Cyclopentanecarboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

20

This material was prepared as described for Example 2 except that cyclopentanecarbonyl chloride (0.048ml) was used. The title compound was a colourless solid (40mg).

LC/MS RT=4.81 min Found ES+ =348

25 ¹H NMR (d6 DMSO, δ) 1.48-1.90 (m,8H) 2.89 (m,1H) 5.24 (d,1H) 7.20-7.68 (m,9H)
8.90 (d,1H) 10.77 (brs,1H)

Example 8

30 Cyclohexanecarboxylic acid 2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

This material was prepared as described for Example 2 except that cyclohexanecarbonyl chloride (0.053ml) was used. The title compound was a colourless solid (57mg).

5 LC/MS RT=5.54 min Found ES+ =362

¹H NMR (d6 DMSO, δ) 1.10-1.43 (5H) 1.60-1.82 (m,5H) 2.44 (m,1H) 5.22 (d,1H) 7.20-7.67 (m,9H) 8.81 (d,1H) 10.75 (s,1H)

Example 9

10

3-Methoxy N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

This material was prepared as described for Example 1 except that 3-methoxybenzoyl chloride (0.056ml) was used. The title compound was a colourless solid (23mg).

LC/MS RT= 5.10min Found ES+ =386

¹H NMR (d6 DMSO, δ) 3.84 (s,3H) 5.51 (d,1H) 7.11-7.71 (m,13H) 9.51 (d,1H) 10.87 (s,1H)

Example 10

4-Methoxy N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

This material was prepared as described for Example 2 except that 4-methoxybenzoyl chloride (68mg) was used. The title compound was a colourless solid (60mg).

30

LC/MS RT= 5.00min Found ES+ =386

¹H NMR (d6 DMSO, δ) 3.83 (s,3H) 5.50 (d,1H) 7.02 (d,2H) 7.21-7.79 (m,9H) 8.02

(d,2H) 9.28 (d,1H) 10.85 (s,1H)

Example 11

5 2-Methoxy N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-
benzamide

This material was prepared as described for Example 2 except that 2-methoxybenzoyl chloride (0.059ml) was used. The title compound was a colourless solid
10 (69mg).

LC/MS RT= 5.12min Found ES+ =386

¹H NMR (d6 DMSO, δ) 4.05 (s,3H) 5.44 (d,1H) 7.11 (t,1H) 7.24-7.70 (m,11H) 7.97
(dd,1H) 9.50 (d,1H) 10.97 (s,1H)

15

Example 12

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-3-trifluoromethylbenzamide

20

This material was prepared as described for Example 2 except that 3-trifluoromethylbenzoyl chloride (0.06ml) was used. The title compound was a colourless solid (88mg).

25 LC/MS RT=5.27 min Found ES+ =424

¹H NMR (d6 DMSO, δ) 5.41 (d,1H) 7.22-7.82 (m,13H) 9.71 (d,1H) 10.86 (brs,1H)

Example 13

30 N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

This material was prepared as described for Example 2 except that benzoyl chloride

(0.046ml) was used. The title compound was a colourless solid (41mg).

LC/MS RT= 4.96min Found ES+ =356

¹H NMR (d6 DMSO, δ) 5.51 (d,1H) 7.22-7.70 (m,12H) 8.03 (m,2H) 9.44 (d,1H)

5 10.87 (s,1H)

Example 14

Thiophene-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-
10 benzo[e][1,4]diazepin-3-yl)-3-amide

This material was prepared as described for Example 2 except that thiophene-2-carbonyl chloride (0.043ml) was used. The title compound was a colourless solid (81mg).

15

LC/MS RT= 4.87min Found ES+ =362

¹H NMR (d6 DMSO, δ) 5.46 (d,1H) 7.19-7.82 (m,11H) 8.20 (m,1H) 9.57 (d,1H)
10.88 (s,1H)

20

Example 15

Furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

25

This material was prepared as described for Example 2 except that furan-2-carbonyl chloride (0.039ml) was used. The title compound was a colourles solid (17mg).

LC/MS RT=4.53 min Found ES+ =346

30 ¹H NMR (d6 DMSO, δ) 5.42 (d,1H) 6.68 (m,1H) 7.24-7.70 (m,10H) 7.90 (m,1H)
9.02 (d,1H) 10.95 (s,1H)

Example 16

Piperidine-1-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

5

This material was prepared as described for Example 2 except that piperidine-1-carbonyl chloride (0.049ml) was used. The title compound was a colourless solid (34mg).

10 LC/MS RT= 4.47min Found ES+ =363

¹H NMR (d6 DMSO, δ) 1.40-1.62 (m,6H) 3.36-3.42 (m,4H) 5.21 (d,1H) 7.20-7.67 (m,10H) 10.76 (s,1H)

Example 17

15

Morpholine-4-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

This material was prepared as described for Example 2 except that morpholine-4-carbonyl chloride (0.046ml) was used. The title compound was a colourless solid (22mg).

20 LC/MS RT= 3.88min Found ES+ =365

25 ¹H NMR (d6 DMSO, δ) 3.36-3.42 (m,4H) 3.55-3.62 (m,4H) 5.21 (d,1H) 7.22-7.67 (m,10H) 10.80 (s,1H)

Example 18

4-Nitro- N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

30

This material was prepared as described for Example 2 except that 4-nitro-benzoyl chloride (74mg) was used. The title compound was a colourless solid (90mg).

LC/MS RT=5.25 min Found ES+ =401

¹H NMR (d6 DMSO, δ) 5.50 (d,1H) 7.23-7.70 (m,9H) 8.25 (d,2H) 8.33 (d,2H) 9.94 (d,1H) 10.92 (s,1H)

5

Example 19

3-Nitro- N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

10 This material was prepared as described for Example 2 except that 3-nitro-benzoyl chloride (74mg) was used. The title compound was a colourless solid (94g).

LC/MS RT= 5.25min Found ES+ =401

¹H NMR (d6 DMSO, δ) 5.51 (d,1H) 7.22-7.85 (m,10H) 8.40-8.48 (m,2H) 8.86 (m,1H) 10.06 (d,1H) 10.91 (s,1H)

Example 20

20 4-Methyl-piperazine-1-carboxylic acid -(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

This material was prepared as described for Example 2 except that 4-methyl-1-piperazinecarbonyl chloride (79mg) was used. The title compound was a colourless solid (35mg).

25 LC/MS RT= 3.29min Found ES- =376

¹H NMR (d6 DMSO, δ) 2.19 (s,3H) 2.28 (m,4H) 3.40 (m,4H) 5.19 (d,1H) 7.19-7.65 (m,10H) 10.75 (s,1H)

Example 21

30

3,4-Dichloro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

This material was prepared as described for Example 2 except that 3,4-dichloro-benzoyl chloride (83mg) was used. The title compound was a colourless solid (42mg).

5

LC/MS RT=3.29 min Found ES+ =424, 426

^1H NMR (d6 DMSO, δ) 5.48 (d,1H) 7.22-7.70 (m,9H) 7.78 (d,1H) 7.98 (dd,1H) 8.31 (d,1H) 9.82 (d,1H) 10.91 (s,1H)

10. Example 22

N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-trifluoromethyl-benzamide

15 This material was prepared as described for Example 2 except that 2-trifluoromethyl-benzoyl chloride (83mg) was used. The title compound was a colourless solid (90mg).

LC/MS RT= 5.47min Found ES+ =424

20 ^1H NMR (d6 DMSO, δ) 5.41 (d,1H) 7.25-7.83 (m,13H) 9.81 (d,1H) 10.93 (s,1H)

Example 23

4-Bromo-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

25

This material was prepared as described for Example 2 except that 4-bromo-benzoyl chloride (87mg) was used. The title compound was a colourless solid (159mg).

LC/MS RT=5.76 min Found ES+ =434, 436

30 ^1H NMR (d6 DMSO, δ) 5.5 (d,1H) 7.23-7.68 (m,9H) 7.72 (d,2H) 7.98 (d,2H) 9.7 (d,1H) 10.94 (s,1H)

Example 24

2-Methyl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

5

This material was prepared as described for Example 2 except that 2-methyl-benzoyl chloride (62mg) was used. The title compound was a colourless solid (113mg).

LC/MS RT= 5.29min Found ES+ =370

10 ^1H NMR (d6 DMSO, δ) 2.42 (s,3H) 5.45 (d,1H) 7.23-7.55 (m,12H) 7.65 (dt,1H) 9.39 (d,1H) 10.90 (s,1H)

Example 25

15 2-Chloro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide
This material was prepared as described for Example 2 except that 2-chloro-benzoyl chloride (70mg) was used. The title compound was a colourless solid (108mg).

LC/MS RT= 5.28min Found ES+ =390, 392

20 ^1H NMR (d6 DMSO, δ) 5.43 (d,1H) 7.26-7.7 (m,13H) 9.71 (d,1H) 10.94 (s,1H)

Example 26

25 2-Nitro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide
This material was prepared as described for Example 2 except that 2-nitro-benzoyl chloride (74mg) was used. The title compound was a colourless solid (50mg).

LC/MS RT=4.94 min Found ES+ =401

10 ^1H NMR (d6 DMSO, δ) 5.42 (d, 1H) 7.25-7.89 (m, 12H) 8.07 (d,1H) 10.05 (d, 1H)
30 10.96 (s, 1H)

Example 27a

2-Methoxy-4-nitro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

5

A mixture of Intermediate 3 (40mg), 2-methoxy-4-nitro-benzoic acid (47mg), triethylamine (0.07ml) and O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (121mg) in dry tetrahydrofuran (3ml) was stirred at 20°C for 18h under a nitrogen atmosphere. The mixture was then partitioned between

10

potassium carbonate solution and dichloromethane. The organic phase was passed through a hydrophobic frit and evaporated. The residue was purified on a silica gel SPE cartridge. Elution with dichloromethane, then with dichloromethane:ethanol: 0.880 ammonia; 400 then 200:8:1 gave an oil which was triturated with diethyl ether giving the title compound as a colourless solid (51mg).

15

LC/MS RT=5.28min Found ES+ = 431

¹H NMR (CDCl₃, δ) 4.09 (s, 3H) 5.69 (d, 1H) 7.08-7.49 (m, 9H) 7.80-7.86 (m, 2H) 8.27 (s, 1H) 8.31(s, 1H) 9.52 (d, 1H)

20

Example 27b

(S)-2-Methoxy-4-nitro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

25

This material was prepared as described for Example 27 except that Intermediate 10 was used in place of Intermediate 3. The title compound was obtained as a colourless solid (37mg)

¹H NMR (DMSO , δ) 4.13 (s, 3H) 5.44 (d, 1H) 7.29-7.70 (m, 9H) 7.97-8.10 (m, 3H)

30

9.63 (d, 1H) 11.05 (s, 1H)

Example 28

Benzo[b]thiophene-3-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

This material was prepared as described for Example 2 except that

5 benzo[b]thiophene-3-carbonyl chloride (39mg) was used. The title compound was a colourless solid (60mg).

LC/MS RT= 5.85min Found ES+ =412

¹H NMR (d6 DMSO, δ) 5.57 (d, 1H) 7.27-7.71 (m, 11H) 8.06 (m, 1H) 8.47 (m, 1H)
10 8.83 (s, 1H) 9.57 (d, 1H) 10.95 (s, 1H)

Example 29

2,3-Dihydro-benzofuran-5-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

This material was prepared as described for Example 2 except that 2,3-dihydro-benzofuran-5-carbonyl chloride (36mg) was used. The title compound was a colourless solid (75mg).

20

LC/MS RT= 5.16min Found ES+ =398

¹H NMR (d6 DMSO, δ) 3.24 (t, 2H) 4.61 (t, 2H) 5.48 (d, 1H) 6.84 (d, 1H) 7.22-7.95
(m, 11H) 9.25 (d, 1H) 10.89 (s, 1H)

25 Example 30

Isoxazole-5-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

30 This material was prepared as described for Example 2 except that isoxazole-5-carbonyl chloride (26mg) was used. The title compound was a colourless solid (22mg).

LC/MS RT= 4.58min Found ES+ =347

¹H NMR (d6 DMSO, δ) 5.44 (d,1H) 7.23-7.72 (m, 10H) 8.80 (d, 1H) 9.98 (d,1H)
11.03 (s,1H)

5

Example 31

Benzo[b]thiophene-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

10

This material was prepared as described for Example 2 except that benzo[b]thiophene-2-carbonyl chloride (39mg) was used. The title compound was a colourless solid (33mg).

15 LC/MS RT=5.90 min Found ES+ =412

¹H NMR (d6 DMSO, δ) 5.49 (d,1H) 7.25-7.72 (m,11H) 7.95-8.07 (m,2H) 8.56 (s,1H) 9.92 (d,1H) 10.96 (s,1H)

Example 32

20

Thiophen-3-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

25 This material was prepared as described for Example 2 except that thiophene-3-carbonyl chloride (29mg) was used. The title compound was a colourless solid (30mg).

LC/MS RT= 4.96min Found ES+ =362

¹H NMR (d6 DMSO, δ) 5.47 (d,1H) 7.23-7.70 (m,11H) 8.48 (m,1H) 9.40 (d,1H)
30 10.91 (s,1H)

Example 33

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-isonicotinamide

5 This material was prepared as described for Example 2 except that isonicotinoyl chloride, hydrochloride (71mg) was used as well as an extra equivalent of triethylamine. The title compound was a colourless solid (22mg).

LC/MS RT= 3.98min Found ES+ =357

10 ^1H NMR (d6 DMSO, δ) 5.50 (d,1H) 7.24-7.70 (m,9H) 7.93 (d,2H) 8.76 (d,2H) 9.89 (d,1H) 10.91 (s,1H)

Example 34

15 N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-nicotinamide

This material was prepared as described for Example 2 except that nicotinoyl chloride, hydrochloride was used as well as an extra equivalent of triethylamine. The title compound was a colourless solid (16mg).

20 LC/MS RT= 3.90min Found ES+ =357
 ^1H NMR (d6 DMSO, δ) 5.51 (d,1H) 7.23-7.70 (m,10H) 8.37 (ddd,1H) 8.75 (dd,1H) 9.15 (d,1H) 9.90 (d,1H) 10.93 (s,1H)

Example 35

25

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-methanesulfonamide

30 This material was prepared as described for Example 2 except that methanesulfonyl chloride (0.031ml) was used. The title compound was a colourless solid (40mg).

LC/MS RT= 4.20min Found ES+ =330

¹H NMR (d6 DMSO, δ) 3.13 (s,3H) 4.81 (brd,1H) 7.22-7.70 (m,9H) 8.43 (brd,1H)
10.95 (brs,1H)

Example 36

5

Propane-1-sulfonic acid-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

This material was prepared as described for Example 2 except that propane-1-sulfonyl chloride (0.054ml) was used. The title compound was a colourless solid (56mg).

LC/MS RT= 4.79min Found ES+ =358

¹H NMR (d6 DMSO, δ) 1.03 (t,3H) 1.84 (m,2H) 3.14 (t,2H) 4.79 (d,1H) 7.23-7.69
15 (m,9H) 8.49 (d,1H) 10.94 (s,1H)

Example 37

Butane-1-sulfonic acid-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

This material was prepared as described for Example 2 except that butane-1-sulfonyl chloride (0.062ml) was used. The title compound was a colourless solid (30mg).

LC/MS RT= 5.18min Found ES+ =372

25 ¹H NMR (d6 DMSO, δ) 0.93 (t,3H) 1.44 (m,2H) 1.80 (m,2H) 3.14 (t,2H) 4.78
(brd,1H) 7.21-7.68 (m,9H) 8.47 (brd,1H) 10.94 (brs,1H)

Example 38

30 2-Bromo-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzenesulfonamide

This material was prepared as described for Example 2 except that 2-bromo-
benzenesulfonyl chloride (122mg) was used. The title compound was a colourless
solid (137mg).

5 LC/MS RT= 5.53min Found ES+ =470, 472

¹H NMR (d6 DMSO, δ) 4.95 (s,1H) 7.03-7.71 (m,12H) 7.88 (m,1H) 8.22 (m,1H)
8.70 (br,1H) 11.04 (s,1H)

Example 39

10

3-Bromo-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-
benzenesulfonamide

This material was prepared as described for Example 2 except that 3-bromo-
15 benzenesulfonyl chloride (122mg) was used. The title compound was a colourless
solid (90mg).

LC/MS RT=5.63 min Found ES+ =470, 472

¹H NMR (d6 DMSO, δ) 4.81 (s,1H) 6.89 (m,2H) 7.20-7.70 (m,9H) 7.82 (m,1H) 7.94
20 (m,1H) 9.3 (br,1H) 10.97 (s,1H)

Example 40

25 4-Bromo-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-
benzenesulfonamide

This material was prepared as described for Example 2 except that 4-bromo-
benzenesulfonyl chloride (122mg) was used. The title compound was a colourless
solid (130mg).

30

LC/MS RT= 5.66min Found ES+ =470, 472

¹H NMR (d6 DMSO, δ) 4.80 (brd,1H) 6.75 (m,2H) 7.20-7.70 (m,7H) 7.78-7.91

(m,4H) 9.40 (brd,1H) 10.95 s,1H)

Example 41

5

2-Fluoro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzenesulfonamide

This material was prepared as described for Example 1 except that 2-fluoro-10 benzenesulfonyl chloride (93mg) was used. The title compound was a colourless solid (140mg).

LC/MS RT= 5.26min Found ES+ =410

¹H NMR (d6 DMSO, δ) 4.94 (d,1H) 7.07 (m,2H) 7.23-7.97 (m,11H) 9.36 (d,1H) 15 10.97 (s,1H)

Example 42

3-(2-Nitro-benzylamino)-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one 20

A solution of Intermediate 3 (50mg) and sodium (triacetoxy)borohydride (106mg) in dichloromethane (6ml) and acetic acid (1ml) was treated with 2-nitro-benzaldehyde (45mg). The resulting mixture was stirred under nitrogen for 18h. Saturated sodium bicarbonate solution was carefully added, and the mixture extracted with dichloromethane. The organic layer was passed through a hydrophobic frit, and 25 evaporated. The residue was then purified on a silica gel SPE cartridge. Gradient elution with 10-18% ethyl acetate in petrol gave the title compound as a colourless solid (33mg)

30 LC/MS RT=4.83 min Found ES+ =387

¹H NMR (d6 DMSO, δ) 3.4 (br, 1H) 4.17 (brs, 1H) 4.31 (q, 2H) 7.15-7.95 (m, 13H) 10.74 (s, 1H)

Example 43

3-(3-Nitro-benzylamino)-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

5 This material was prepared as described for Example 42 except that 3-nitrobenzaldehyde (45mg) was used. The title compound was a colourless solid (32mg).
LC/MS RT=4.95 min Found ES+ =387

10 ^1H NMR (d6 DMSO, δ) 3.45 (br, 1H) 4.16 (brs, 1H) 4.23 (brm, 2H) 7.15-7.63 (m, 10H) 7.85 (d, 1H) 8.08 (dd, 1H) 8.30 (s, 1H) 10.76 (s, 1H)

Example 44

3-(4-Nitro-benzylamino)-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

15 This material was prepared as described for Example 42 except that 4-nitrobenzaldehyde (45mg) was used. The title compound was a colourless solid (33mg).

20 LC/MS RT=4.88 min Found ES+ =387
 ^1H NMR (d6 DMSO, δ) 3.42 (br, 1H) 4.11-4.30 (brm, 3H) 7.16-7.63 (m, 9H) 7.70 (d, 2H) 8.20 (d, 2H) 10.77 (s, 1H)

Example 45

25 3-(2-Methoxy-benzylamino)-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

This material was prepared as described for Example 42 except that 2-methoxybenzaldehyde (41mg) was used. The title compound was a colourless solid (48mg).

30 LC/MS RT=4.95 min Found ES+ =372
 ^1H NMR (d6 DMSO, δ) 3.73 (s, 3H) 3.97 (q, 2H) 4.17 (s, 1H) 6.85-6.96 (m, 2H) 7.15-7.63 (m, 11H) 10.72 (s, 1H)

Example 46

3-(3-Methoxy-benzylamino)-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

5

This material was prepared as described for Example 42 except that 3-methoxy-benzaldehyde (41mg) was used. The title compound was a colourless solid (43g).

LC/MS RT=5.03 min Found ES+ =372

10 ^1H NMR (d6 DMSO, δ) 3.71 (s, 3H) 3.81-4.18 (m, 3H) 6.74 (m, 1H) 6.80-6.86 (m, 2H) 7.15-7.64 (m, 10H) 10.74 (s, 1H)

Example 47

15 5-Phenyl-3-(2-trifluoromethyl-benzylamino)-1,3-dihydro-benzo[e][1,4]diazepin-2-one

This material was prepared as described for Example 42 except that 2-trifluoromethyl-benzaldehyde (52mg) was used. The title compound was a colourless 20 solid (29mg).

LC/MS RT=5.02 min Found ES+ =410

^1H NMR (d6 DMSO, δ) 4.18 (s, 1H) 4.23 (brs, 2H) 7.15-7.70 (m, 12H) 7.91 (d, 1H) 10.76 (s, 1H)

25

Example 48

5-Phenyl-3-(3-trifluoromethyl-benzylamino)-1,3-dihydro-benzo[e][1,4]diazepin-2-one

30

This material was prepared as described for Example 42 except that 3-trifluoromethyl-benzaldehyde (52mg) was used. The title compound was a colourless

solid (34mg).

LC/MS RT= 5.28min Found ES- =408

¹H NMR (d6 DMSO, δ) 4.12 (q, 2H) 4.18 (s, 1H) 7.15-7.78 (m, 13H) 10.74 (s, 1H)

5

Example 49

5-Phenyl-3-(4-trifluoromethyl-benzylamino)-1,3-dihydro-benzo[e][1,4]diazepin-2-one

10

This material was prepared as described for Example 42 except that 4-trifluoromethyl-benzaldehyde (52mg) was used. The title compound was a colourless solid (25mg).

15 LC/MS RT= 5.27min Found ES-=408

¹H NMR (d6 DMSO, δ) 4.13 (q, 2H) 4.20 (s, 1H) 7.15-7.70 (m, 13H) 10.76 (s, 1H)

Example 50

20 3-[(Furan-2-ylmethyl)-amino]-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

This material was prepared as described for Example 42 except that 2-furaldehyde (29mg) was used. The title compound was a colourless solid (56mg).

25 LC/MS RT=4.07 min Found ES+ =332

¹H NMR (d6 DMSO, δ) 3.05 (m, 1H) 3.80-4.13 (m, 2H) 4.18 (d, 1H) 6.19 (brs, 1H) 6.32 (brs, 1H) 7.15-7.65 (m, 10H)

Example 51

30

N-(7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-acetamide

This material was prepared as described for Example 1 except that Intermediate 6 (57mg) was used. The title compound was a colourless solid (17mg).

LC/MS RT=4.21 min Found ES+ =328, 330

5 ^1H NMR (d6 DMSO, δ) 3.34 (s, 3H) 5.26 (d, 1H) 7.28-7.31 (m, 2H) 7.31-7.58 (m, 5H) 7.71 (dd, 1H) 9.14 (d, 1H) 10.96 (s, 1H)

Example 52

10 N-(7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-isobutyramide

This material was prepared as described for Example 2 except that Intermediate 6 and isobutyl chloride (0.021ml) was used. The title compound was a colourless solid 15 (49mg).

LC/MS RT=4.78 min Found ES+ =356, 358

^1H NMR (d6 DMSO, δ) 1.04 (d, 6H) 2.72 (septet, 1H) 5.27 (d, 1H) 7.29-7.55 (m, 7H) 7.71 (dd, 1H) 9.00 (d, 1H) 10.92 (s, 1H)

20

Example 53

N-(7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-methanesulfonamide

25

This material was prepared as described for Example 2 except that Intermediate 6 and methanesulfonyl chloride (0.015ml) were used. The title compound was a colourless solid (18mg).

30 LC/MS RT= 4.61min Found ES+ =364, 366

^1H NMR (d6 DMSO, δ) 3.13 (s, 3H) 4.85 (brd, 1H) 7.29-7.58 (m, 7H) 7.71 (dd, 1H) 8.46 (brd, 1H) 11.04 (brs, 1H)

Example 54

Furan-2-carboxylic acid (7-chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

5

This material was prepared as described for Example 2 except that Intermediate 6 and 2-furancarbonyl chloride (0.020ml) were used. The title compound was a colourless solid (50mg).

10 LC/MS RT=5.07 min Found ES+ =380, 382

¹H NMR (d6 DMSO, δ) 5.45 (d, 1H) 6.68 (m, 1H) 7.28-7.70 (m, 7H) 7.73 (dd, 1H) 7.91 (m, 1H) 9.15 (d, 1H) 11.07 (s, 1H)

Example 55

15

Thiophene-2-carboxylic acid (7-chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

20 This material was prepared as described for Example 2 except that Intermediate 6 and 2-thiophenecarbonyl chloride (0.021ml) were used. The title compound was a colourless solid (49mg).

LC/MS RT=5.40 min Found ES+ =396, 398

¹H NMR (d6 DMSO, δ) 5.49 (d, 1H) 7.22-7.83 (m, 10H) 8.21 (dd, 1H) 9.67 (d, 1H) 25 11.04 (s, 1H)

Example 56

30 Cyclohexanecarboxylic acid (7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

This material was prepared as described for Example 2 except that Intermediate 6

and cyclohexanecarbonyl chloride (0.027) were used. The title compound was a colourless solid (52mg).

LC/MS RT=5.61 min Found ES+ =396, 398

5 ^1H NMR (d6 DMSO, δ) 1.2-1.33 (m, 5H) 1.60-1.83 (m, 5H) 2.45 (m, 1H) 5.25 (d, 1H) 7.27-7.73 (m, 8H) 8.93 (d, 1H) 10.92 (s, 1H)

Example 57

10 N-(7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-methoxy-benzamide

This material was prepared as described for Example 2 except that Intermediate 6 and 2-methoxy-benzoyl chloride (0.030ml) were used. The title compound was a colourless solid (55mg).

LC/MS RT=5.58 min Found ES+ =420, 422

^1H NMR (d6 DMSO, δ) 4.05 (s, 3H) 5.47 (d, 1H) 7.12 (t, 1H) 7.25-7.61 (m, 9H) 7.72 (dd, 1H) 7.98 (dd, 1H) 9.54 (d, 1H) 11.14 (s, 1H)

20

Example 58

N-(7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-4-methoxy-benzamide

25

This material was prepared as described for Example 2 except that Intermediate 6 and 4-methoxy-benzoyl chloride (0.027ml) were used. The title compound was a colourless solid (61mg).

30 LC/MS RT=5.48 min Found ES+ =420, 422

^1H NMR (d6 DMSO, δ) 3.84 (s, 3H) 5.53 (d, 1H) 7.03 (d, 2H) 7.31-7.59 (m, 8H) 8.04 (d, 2H) 9.39 (d, 1H) 11.01 (s, 1H)

Example 59

N-(7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-nitrobenzamide

5

This material was prepared as described for Example 2 except that Intermediate 6 and 2-nitro-benzoyl chloride (0.027) were used. The title compound was a colourless solid (61mg).

10 LC/MS RT=5.25 min Found ES+ =435, 437

¹H NMR (d6 DMSO, δ) 5.45 (d, 1H) 7.36-7.88 (m, 11H) 8.07 *d, 1H) 10.03 (d, 1H) 11.03 (s, 1H)

Example 60

15

2-(2-Methoxy-phenyl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-acetamide

This material was prepared as described for Example 2 except that (2-methoxy-phenyl)-acetyl chloride (33mg) was used. The title compound was a colourless solid (13mg).

20 LC/MS RT=4.98 min Found ES+ =400

¹H NMR (d6 DMSO, δ) 3.63 (s, 2H) 3.79 (s, 3H) 5.25 (d, 1H) 6.89-6.99 (m, 2H) 25 7.20-7.33 (m, 5H) 7.45-7.68 (m, 6H) 9.01 (d, 1H) 10.87 (s, 1H)

Example 61

2-(3-Methoxy-phenyl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-acetamide

This material was prepared as described for Example 2 except that (3-methoxy-

phenyl)-acetyl chloride (33mg) was used. The title compound was a colourless solid (12mg).

LC/MS RT=4.95 min Found ES+ =400

5 ^1H NMR (d6 DMSO, δ) 3.62 (m, 2H) 3.75 (s, 3H) 5.23 (d, 1H) 6.78-6.96 (m, 3H)
7.19-7.70 (m, 10H) 9.33 (d, 1H) 10.86 (s, 1H)

Example 62

10 2-(4-Methoxy-phenyl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-acetamide

This material was prepared as described for Example 2 except that (4-methoxy-phenyl)-acetyl chloride (33mg) was used. The title compound was a colourless solid
15 (20mg).

LC/MS RT=4.86 min Found ES+ =400

^1H NMR (d6 DMSO, δ) 3.58 (s, 2H) 3.73 (s, 3H) 5.22 (d, 1H) 6.87 (d, 2H) 7.23-7.71
(m, 11H) 9.25 (d, 1H) 10.85 (s, 1H)

20

Example 63

2-(4-Nitro-phenyl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-acetamide

25

This material was prepared as described for Example 2 except that (4-nitro-phenyl)-acetyl chloride (36mg) was used. The title compound was a colourless solid (18mg).

LC/MS RT=5.03 min Found ES+ =415

30 ^1H NMR (d6 DMSO, δ) 3.86 (s, 2H) 5.24 (d, 1H) 7.24-7.70 (m, 11H) 8.19 (d, 2H)
9.53 (d, 1H) 10.88 (s, 1H)

Example 64

2-(3-Nitro-phenyl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-acetamide

5

This material was prepared as described for Example 2 except that (3-nitro-phenyl)-acetyl chloride (36mg) was used. The title compound was a colourless solid (25mg).

LC/MS RT=5.02 min Found ES+ =415

10 ^1H NMR (d6 DMSO, δ) 3.86 (s, 2H) 5.24 (d, 1H) 7.24-7.67 (m, 10H) 7.89 (d, 1H)
8.12 (dd, 1H) 8.26 (s, 1H) 9.53 (d, 1H) 10.89 (s, 1H)

Example 65

15 N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-(2-trifluoromethyl-phenyl)-acetamide

This material was prepared as described for Example 2 except that (2-trifluoromethyl-phenyl)-acetyl chloride (41mg) was used. The title compound was a
20 colourless solid (9mg).

LC/MS RT= 5.43min Found ES+ =438

^1H NMR (d6 DMSO, δ) 3.92 (s, 2H) 5.26 (d, 1H) 7.24-7.70 (m, 13H) 9.41 (d, 1H)
10.87 (s, 1H)

25

Example 66

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-(3-trifluoromethyl-phenyl)-acetamide

30

This material was prepared as described for Example 2 except that 3-trifluoromethyl-phenyl)-acetyl chloride (41mg) was used. The title compound was a colourless solid

(20mg).

LC/MS RT= 5.56min Found ES+ =438

¹H NMR (d6 DMSO, δ) 3.80 (s, 2H) 5.24 (d, 1H) 7.24-7.75 (m, 13H) 9.49 (d, 1H)

5 10.89 (s, 1H)

Example 67

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-(4-

10 trifluoromethyl-phenyl)-acetamide

This material was prepared as described for Example 2 except that (4-trifluoromethyl-phenyl)-acetyl chloride (41mg) was used. The title compound was a colourless solid (13mg).

15

LC/MS RT= 5.57min Found ES+ =438

¹H NMR (d6 DMSO, δ) 3.79 (s, 2H) 5.23 (d, 1H) 7.24-7.70 (m, 13H) 9.48 (d, 1H)

10.87 (s, 1H)

20 Example 68

1-(2-Methoxy-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea

25 A solution of 2-methoxy-aniline (37mg) in dry dichloromethane (3ml) was treated with triethylamine (0.04ml) followed by 20% phosgene in toluene (0.08ml). The mixture was stirred at room temperature for 1h, and then Intermediate 3 (37mg) was then added, and the stirring continued for 18h. The mixture was partitioned between water and ethyl acetate. The organic layer was passed through a hydrophobic frit and
30 evaporated and the residue was purified on a silica gel SPE cartridge. Gradient elution with 0-5% methanol in dichloromethane gave the title compound as a colourless solid (24mg).

LC/MS RT=5.05 min Found ES+ =401

¹H NMR (d6 DMSO, δ) 3.86 (s, 3H) 5.21 (d, 1H) 6.78-7.02 (m, 3H) 7.23-7.70 (m, 9H) 7.98 (m 1H) 8.26 (d, 1H) 8.60 (s, 1H) 10.89 (s, 1H)

5

Example 69

1-(2-Nitro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea

10

This material was prepared as described for Example 68 except that 2-nitro-aniline (21mg) was used. The title compound was a yellow solid (23mg).

LC/MS RT=5.30 min Found ES+ =416

¹H NMR (d6 DMSO, δ) 5.19 (d, 1H) 7.15-7.70 (m, 11H) 8.05 (dd, 1H) 8.17 (d, 1H)

15 8.82 (d, 1H) 9.68 (s, 1H) 10.95 (s, 1H)

Example 70

1-(2-Chloro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea

20

This material was prepared as described for Example 68 except that 2-chloro-aniline (0.017 ml) was used. The title compound was a colourless solid (21mg).

25 LC/MS RT=5.34 min Found ES+ =405

¹H NMR (d6 DMSO, δ) 5.21 (d, 1H) 6.94-7.70 (m, 12H) 8.08 (m, 1H) 8.47 (d, 1H) 8.57 (s, 1H) 10.93 (s, 1H)

Example 71

30

1-(4-Chloro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea

A mixture of Intermediate 3 (30mg) and 4-chloro-1-isocyanato-benzene (0.011ml) in dry THF (4ml) was treated with triethylamine (0.05ml). The mixture was stirred at room temperature for 18h, and was then partitioned between water and dichloromethane. The organic layer was passed through a hydrophobic frit, and was then evaporated. The residue was triturated with petroleum ether giving the title compound as a beige solid (34mg).

5 LC/MS RT= 5.45min Found ES+ =405
10 ^1H NMR (d6 DMSO, δ) 5.17 (d, 1H) 7.25-7.70 (m, 14H) 9.18 (s, 1H) 10.95 (s, 1H)

Example 72

15 1-(2- oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-3-p-tolyl-urea
This material was prepared as described for Example 71 except that 1-isocyanato-4-methyl-benzene (0.011ml) was used. The title compound was an off-white solid (32mg).

20 LC/MS RT=5.18 min Found ES+ =385
 ^1H NMR (d6 DMSO, δ) 2.22 (s, 3H) 5.19 (d, 1H) 7.05 (d, 2H) 7.23-7.70 (m, 12H) 8.92 (s, 1H) 10.92 (s, 1H)

Example 73a

25 1-(2-Fluoro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea

30 This material was prepared as described for Example 71 except that 2-fluoro-1-isocyanato-benzene (0.010 ml) was used. The title compound was a beige solid (29mg).

LC/MS RT= 5.09min Found ES+ =389

¹H NMR (d6 DMSO, δ) 5.21 (d, 1H) 6.90-7.70 (m, 12H) 8.07 (m, 2H) 8.93 (s, 1H) 10.94 (s, 1H)

Example 73b

5

(S)-1-(2-Fluoro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea

This material was prepared as described for Example 73 except that Intermediate 10
10 was used. The title compound was a colourless solid (33mg).

¹H NMR (DMSO, δ) 5.24 (d, 1H) 6.90-7.75 (m, 12H) 8.11-8.17(m, 2H) 8.95 (d, 1H) 10.95 (s, 1H)

15 Example 74

1-(4-Fluoro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea

20 This material was prepared as described for Example 71 except that 4-fluoro-1-isocyanato-benzene (0.010ml) was used. The title compound was an off-white solid (26mg).

LC/MS RT= 5.02min Found ES+ =389

¹H NMR (d6 DMSO, δ) 5.18 (d, 1H) 7.08 (t, 2H) 7.25-7.70 (m, 12H) 9.07 (s, 1H)
25 10.94 (s, 1H)

Example 75a

4-Methanesulfonyl-2-methoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide.

This material was prepared as described for Example 27 except that 4-

methanesulfonyl-2-methoxy-benzoic acid (69mg) was used. The title compound was a colourless solid (54mg).

5 ¹H NMR (DMSO, δ) 3.33 (s, 3H) 4.13 (s, 3H) 5.44 (d, 1H) 7.33-7.71 (m, 11H) 8.10
(d, 1H) 9.61 (d, 1H) 11.06 (s, 1H)

Example 75b

10 (S)- 4-Methanesulfonyl-2-methoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-
benzo[e][1,4]diazepin-3-yl)-benzamide.

This material was prepared as described for Example 76b except that 4-methanesulfonyl-2-methoxy-benzoic acid (46mg) was used. The title compound was a colourless solid (55mg)

15 ¹H NMR (DMSO, δ) 3.33 (s, 3H) 4.13 (s, 3H) 5.44 (d, 1H) 7.33-7.71 (m, 11H) 8.10
(d, 1H) 9.61 (d, 1H) 11.06 (s, 1H)

Example 76a

20 5-Acetyl-2-ethoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-
benzamide

This material was prepared as described for Example 27 except that 5-acetyl-2-ethoxy-benzoic acid (41mg) was used. The title compound was a colourless solid (45mg)

25 ¹H NMR (DMSO, δ) 1.59 (t, 3H) 2.59 (s, 3H) 4.42 (q, 2H) 5.44 (d, 1H) 7.30-7.54
(m, 10H) 8.17 (ddd, 1H) 8.58 (d, 1H) 9.71 (d, 1H) 11.07 (s, 1H)

30

Example 76b

5 (S)- 5-Acetyl-2-ethoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

This material was prepared as described for Example 76b except that 5-acetyl-2-ethoxy-benzoic acid (83mg) was used. The title compound was a colourless solid
10 (108mg)

¹H NMR (DMSO, δ) 1.59 (t, 3H) 2.59 (s, 3H) 4.42 (q, 2H) 5.44 (d, 1H) 7.30-7.54 (m, 10H) 8.17 (ddd, 1H) 8.58 (d, 1H) 9.71 (d, 1H) 11.07 (s, 1H)

15 Example 77a

6-Fluoro-4H-benzo[1,3]dioxine-8-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

20 This material was prepared as described for Example 27 except that 6-fluoro-4H-benzo[1,3]dioxine-8-carboxylic acid (36.2mg) was used. The title compound was a colourless solid (40mg)

¹H NMR (DMSO, δ) 5.02 (s, 2H) 5.42 (d, 1H) 5.54 (s, 2H) 7.26-7.70 (m, 12H) 9.37 (d, 1H) 11.06 (s, 1H)

Example 77b

30 (S)- 6-Fluoro-4H-benzo[1,3]dioxine-8-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

This material was prepared as described for Example 76b except that 6-fluoro-4H-

benzo[1,3]dioxine-8-carboxylic acid (86mg) was used. The title compound was a colourless solid (65mg)

¹H NMR (DMSO, δ) 5.02 (s, 2H) 5.42 (d, 1H) 5.54 (s, 2H) 7.26-7.70 (m, 12H) 9.37 (d, 1H) 11.06 (s, 1H)

5

Example 78

(S)-2-Methoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-4-trifluoromethyl-benzamide

10

This material was prepared as described for Example 76b except that 2-methoxy-4-trifluoromethyl-benzoic acid (26mg) was used. The title compound was a colourless solid (32mg).

15 ¹H NMR (DMSO, δ) 4.12 (s, 3H) 5.44 (d, 1H) 7.30-7.68 (m, 11H) 8.09 (d, 1H) 9.59 (d, 1H) 11.06 (s, 1H)

Example 79a

20 2,4,5-Trifluoro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

This material was prepared as described for Example 27 except that 2,4,5-trifluoro-benzoic acid (39mg) was used. The title compound was a colourless solid (56mg).

25 ¹H NMR (DMSO, δ) 5.42 (d, 1H) 7.29-7.85 (m, 11H) 9.43-9.47 (m, 1H) 11.02 (s, 1H)

Example 79b

30 (S)-2,4,5-Trifluoro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

This material was prepared as described for Example 75b except that 2,4,5-trifluoro-

benzoic acid (70mg) was used. The title compound was a colourless solid (74mg).

¹H NMR (DMSO, δ) 5.42 (d, 1H) 7.29-7.85 (m, 11H) 9.43-9.47 (m, 1H) 11.02 (s, 1H)

5

Example 80a

2-Hydroxy- N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

10

This material was prepared as described for Example 27 except that 2-hydroxy-benzoic acid (30mg) was used. The title compound was a colourless solid (40mg).

¹H NMR (DMSO, δ) 5.47 (d, 1H) 6.92 (t, 1H) 7.00 (d, 1H) 7.34-7.66 (m, 10H) 8.01 (dd, 1H) 10.07 (brs, 1H) 11.01 (s, 1H)

Example 80b

(S)-2-Hydroxy- N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

This material was prepared as described for Example 75b except that 2-hydroxy-benzoic acid (55mg) was used. The title compound was a colourless solid (63mg).

25 ¹H NMR (DMSO, δ) 5.48 (d, 1H) 6.95 (t, 1H) 7.04 (d, 1H) 7.28-7.70 (m, 10H) 8.06 (dd, 1H) 9.94 (d, 1H) 11.02 (s, 1H) 11.74 (brs, 1H)

Example 81a

30 1H-Indole-7-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

This material was prepared as described for Example 27 except that 1H-indole-7-carboxylic acid (35mg) was used. The title compound was a colourless solid (49mg).

¹H NMR (DMSO, δ) 5.65 (d, 1H) 6.54 (m, 1H) 7.17-8.10 (m, 13H) 9.56 (d, 1H)

5

Example 81b

(S)-1H-Indole-7-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

10

This material was prepared as described for Example 75b except that 1H-indole-7-carboxylic acid (64mg) was used. The title compound was a colourless solid (69mg).

¹H NMR (DMSO, δ) 5.65 (d, 1H) 6.54 (m, 1H) 7.17-8.10 (m, 13H) 9.56 (d, 1H)

15

Example 82a

3-Methoxy-naphthalene-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

20

This material was prepared as described for Example 27 except that 3-methoxy-naphthalene-2-carboxylic acid (40mg) was used. The title compound was a colourless solid (73mg).

25 ¹H NMR (DMSO, δ) 4.15 (s, 3H) 5.51 (d, 1H) 7.37-7.63 (m, 12H) 7.95 (d, 1H) 8.03 (d, 1H) 8.58 (s, 1H) 9.69 (d, 1H) 11.05 (s, 1H)

Example 82b

30 (S)-3-Methoxy-naphthalene-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

This material was prepared as described for Example 75b except that 3-methoxy-naphthalene-2-carboxylic acid (80mg) was used. The title compound was a colourless solid (113mg).

5 ^1H NMR (DMSO, δ) 4.15 (s, 3H) 5.51 (d, 1H) 7.31-7.68 (m, 12H) 7.95 (d, 1H) 8.03 (d, 1H) 8.58 (s, 1H) 9.71 (d, 1H) 11.08 (s, 1H)

Using analogous procedures to those outlined above, the following compounds were also prepared:

10 Example 83 N-[7-Chloro-5-(2-fluoro-phenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepine-3-yl]-4-methoxoy-benzamide

Example 84 1-(2-Fluoro-benzyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea

Example 85 1-(4-Methoxy-benzyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea

Example 86 1-(3-Methyl-benzyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea

Example 87 1-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-3-(4-trifluoromethyl-phenyl)-urea

20 Example 88 4-Chloro-2-methoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

Example 89 4-Methoxy-3-nitro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)benzamide

Example 90 3-Methoxy-2-nitro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

Example 91 5-Chloro-2-methoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)benzamide

Example 92 5-Fluoro-2-methoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

30 Example 93 2-Methoxy-4-nitro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

Example 94 5-Methoxy-2-nitro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-

benzo[e][1,4]diazepin-3-yl)-benzamide

Example 95 3-Methoxy-4-nitro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

Example 96 3-(2-Methoxy-phenyl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-5 benzo[e][1,4]diazepin-3-yl)propionamide

Example 97 3-(3-Methoxy-phenyl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-propionamide

Example 98 3-(4-Methoxy-phenyl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-propionamide

10 Example 99 N-[5-(3-Chloro-phenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-2-methoxy-benzamide

Example 100 N-[5-(3-Chloro-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-4-methoxy-benzamide

Example 101 N-[5-(3-Chloro-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-15 benzo[e][1,4]diazepin-3-yl]-2-nitro-benzamide

Example 102 N-[5-(3-Chloro-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-4-nitro-benzamide

Example 103 4-Methoxy-N-[2-oxo-5-(4-trifluoromethyl-phenyl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-benzamide

20 Example 104 2-Methoxy-N-[2-oxo-5-(3-trifluoromethyl-phenyl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-benzamide

Example 105 4-Methoxy-N-[2-oxo-5-(3-trifluoromethyl-phenyl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-benzamide

Example 106 2-Ethoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-25 3-yl)-benzamide

Example 107 2,4-Dimethoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

Example 108 2-Bromo-5-methoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

30 Example 109 2-Methoxy-N-[5-(3-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-benzamide

Example 110 N-[5-(3-Methoxy-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-4-nitro-benzamide

Example 111 2-Methoxy-N-(8-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-5 benzo[e][1,4]diazepin-3-yl)-benzamide

Example 112 2-Chloro-4-methanesulfonyl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

Example 113 2-Dimethylamino-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

10 Example 114 (2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-carbamic acid benzyl ester

Example 115 1-(3,5-Dimethyl-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea

Example 116 1-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-3-(4-15 trifluoromethoxy-phenyl)-urea

Example 117 1-(4-Bromo-2-trifluoromethyl-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea

Example 118 1-(4-Bromo-benzyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea

20 Example 119 1-(2,3-Dichloro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea

Example 120 1-(2,6-Dimethyl-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea

Example 121 1-(2-Chloro-6-methyl-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-25 benzo[e][1,4]diazepin-3-yl)-urea

Example 122 1-(4-Nitro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea

Example 123 1-(2-Methylsulfanyl-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea

30 Example 124 1-(2,6-Dichloro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea

Example 125 5-tert-Butyl-2-methoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-

benzo[e][1,4]diazepin-3-yl)-benzamide

Example 126 2,5-Dimethoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

Example 127 1-(2,6-Difluoro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-

5 benzo[e][1,4]diazepin-3-yl)-urea

Example 128 1-(3-Fluoro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea

Example 129 1-(3-Methoxy-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea

10 Example 130 1-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-3-(3-trifluoromethyl-phenyl)-urea

Example 131 1-(3-Chloro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea

Example 132 2-Methoxy-4-methylsulfanyl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-

15 benzo[e][1,4]diazepin-3-yl)-benzamide

Example 133 4-Methanesulfonyl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

Example 134 N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)terephthalamic acid methyl ester

20 Example 135 2-Fluoro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

Example 136 2,6-Difluoro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

Example 137 N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-

25 propoxy-benzamide

Example 138 2-Iodo-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

Example 139 3-Methoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-terephthalamic acid méthyl ester

30 Example 140 4-Amino-5-chloro-2-methoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

Example 141 1-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-3-m-

tolyl-urea

Example 142 2-Methylsulfanyl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

Example 143 2-Methoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-

5 benzo[e][1,4]diazepin-3-yl)-5-sulfamoyl-benzamide

Example 144 2-Hydroxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-3-phenyl-propionamide

Example 145 3-Hydroxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-3-phenyl-propionamide

10 Example 146 3-(2-Fluoro-phenyl)-1-methyl-1-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea

Example 147 2-Methoxy-N-methyl-4-nitro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

Example 148 1-tert-Butyl-3-(2-oxo-5-phenyl-2,3-dihydro-1H-

15 benzo[e][1,4]diazepin-3-yl)-urea

Example 149 1-Cyclohexyl-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea

Example 150 1-Ethyl-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea

20 Example 151 1-Butyl-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea

Example 152 4,5-Dimethyl-furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)amide

Example 153 Piperidine-1-carboxylic acid (7-chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

25 Example 154 N-[5-(3-Chloro-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]acetamide

Example 155 N-[5-(3-Chloro-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-isobutyramide

30 Example 156 Furan-2-carboxylic acid [5-(3-chloro-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-amide

Example 157 Thiophene-2-carboxylic acid [5-(3-chloro-phenyl)-2-oxo-5-phenyl-

2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-amide

Example 158 Cyclohexanecarboxylic acid [5-(3chloro-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-amide

Example 159 Piperidine-1-carboxylic acid [5-(3-chloro-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-amide

Example 160 N-[5-(3-Chloro-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]isonicotinamide

Example 161 5-Methyl-furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

Example 162 Pyrazine-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

Example 163 N-[5-(3-Methoxy-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-isobutyramide

Example 164 Thiophene-2-carboxylic acid [5-(3-methoxy-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-amide

Example 165 Cyclohexanecarboxylic acid [5-(3-methoxy-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-amide

Example 166 Piperidine-1-carboxylic acid [5-(3-methoxy-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-amide

Example 167 Piperidine-4-carboxylic acid [5-(3-methoxy-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-amide

Example 168 Cyclohexanecarboxylic acid (8-chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

Example 169 Thiophene-2-carboxylic acid (8-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

Example 170 1-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-3-thiophene-2-yl-urea

Example 171 1-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-3-thiophene-3-yl-urea

Example 172 Pyridine-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

Example 173 1H-Pyrazole-4-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-

benzo[e][1,4]diazepin-3-yl)-amide

Example 174 6-Dimethylamino-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-nicotinamide

Example 175 2-Ethoxy-naphthalene-1-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

Example 176 9-Oxo-9H-fluorene-1-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

Example 177 2-Oxo-2,3-dihydro-benzimidazole-1-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

Example 178 (2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)carbamic acid tert-butyl ester

Example 179 (S)-4,5-Dibromo-furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

Example 180 (S)-Benzofuran-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

Example 181 (2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-carbamic acid methyl ester

Example 182 (2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-carbamic acid ethyl ester

Example 183 (2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-carbamic acid isobutyl ester

Example 184 2-Oxo-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-thiophene-2-yl-acetamide

25 Activity Example 1

Examples 1 to 74 and 83 to 124 were tested using the following protocol.

XTT Assay Protocol

30 The inner 60 wells of 96 well tissue culture plates were seeded with Vero cells at 3×10^4 cells/well (1×10^4 cells/well for toxicity studies) in 100 or 150 μ l of medium

and incubated at 37°C overnight or until nearing confluence. For primary screen, 25 µl compounds were added directly to 100 µl medium in single wells to duplicate plates. A third plate was prepared for simultaneous toxicity investigation.

- 5 For follow up investigation, 70 µl of compound in duplicate wells were added directly to culture medium at 3.2x final concentration and ½ log serially diluted down columns of plate. A duplicate plate was prepared for simultaneous toxicity investigation.
- 10 Cells were infected with 25 µl RSV to give m.o.i. \approx 0.2. Some 100 µl of sterile distilled water were added to the outer wells of the plate and incubated at 33°C for 6 days. Some 0.25 µl/ml PMS were added to stock XTT solution, final conc. 25 µM PMS. Then 25 µl warmed XTT/PMS solution were added to each well and incubated for 5 hours at 37°C. Plates were shaken (DynaTech Vari-Shaker) vigorously for 10
- 15 mins and allowed to cool for 15 mins before sealing. Absorbance at 450 nM was measured and data analysed using Microsoft Excel software.

Maximum OD_{450nm} reading (uninfected, untreated control cells) corresponded to 100% inhibition. Minimum OD_{450nm} readings (infected control cells) corresponded to 0% inhibition. Log10 concentration was plotted against OD_{450nm} and IC₅₀ (Table 1) values were calculated from either reading 50% value from graph or using regression analysis.

Examples 75 to 82 and 125 to 184 were tested according to the protocol described

25 below.

XTT Assay Protocol

The inner 60 wells of 96 well tissue culture plates were seeded with Hep-2 cells at

30 4x10⁴ cells/well for compound activity and toxicity studies in 100µl of medium and incubated at 37°C overnight or until nearing confluence.

Cells were infected with 25 μ l RSV previously titrated to give 80% cell kill. To each well 25 μ M of test compound were added. The final DMSO concentration was 0.5%. Some 200 μ l of sterile distilled water were added to the outer wells of the plate and incubated at 37°C for 6 days. Some 0.25 μ l/ml PMS were added to stock XTT 5 solution, final conc. 25 μ M PMS. Then 25 μ l warmed XTT/PMS solution were added to each well and incubated for 1 hour at 37°C.

Maximum OD_{450nm} reading (uninfected, untreated control cells) corresponded to 100% inhibition. Minimum OD_{450nm} readings (infected control cells) corresponded to 10 0% inhibition. Log₁₀ concentration was plotted against OD_{450nm} and IC₅₀ values were calculated from either reading 50% value from graph or using regression analysis.

The LC-MS data for Examples 75a to 184 is also shown in Table 2.

15

Table 1

Example	XTT IC50 (uM)	TD50 (2d)	TD50 (6d)
1			
2	4		
3	2.5		
4	5		
5	2.5		
6	6		
7	2		
8	2		
9	2	70	100
10	1.5		
11	0.5	100	
12	2.5		
13	1.5	100	
14	1.5	100	
15	1		
16	2		
17	5		
18	2		
19	2	100	100
20	25		
21	6	100	100
22	4		
23	5		
24	3		
25	2		
26	2		
27a	0.3	100	
27b	<0.3		>100
28	5		
29	2		
30	3		
31	5		
32	2		

33	2.5		
34	3		
35	6		
36	15		
37	15		
38	6	50	40
39	10	60	50
40	10	50	15
41	10	100	100
42	20		
43	30		
44	10		
45	20		
46	30		
47	30	100	50
48		100	50
49	50	100	100
50	50		
51	5		
52	3		
53	5		
54	1.5		30
55	3		30
56	5		
57	0.7		
58	1.2		30
59	5		
60	5		
61	3		
62	1.5		
63	1.7		
64	1		
65	2		100
66	1.5		30
67	1.5		100
68	1		
69	1.5		

70	1.5		100
71	3		50
72	1.5		100
73a	1		100
73b	0.7		>50
74	1.5		100

Table 2

Example No	LC-MS data		XTT IC50 (uM)	TC50 (2d)	TC50 (6d)
	RT/min	ES			
75a	4.82	ES+ 464.33	2.4		
75b	4.83	ES+ 464	0.6		>50
76a	5.2	492	3.5		64
76b	4.81	ES+ 442.49	1.2		>50
77a	5.28	ES+ 432	4.6		>50
77b	4.85	ES+ 432.46	0.5		33.2
78	5.62	ES+ 454	2.7		32.5
79a			8		65
79b	5.03	ES+ 410.44	5.8		>50
80a			8.7		33
80b	4.83	ES+ 372.50	2		>50
81a	5.39	ES+ 395.46	8.4		63
81b	5.01	ES+ 395.46	1.2		35.6
82a			6.7		>50
82b	5.21	ES+ 436.49	1.5		>50
83	5.37	438.44, 436.39	6	>100	32
84	4.74	ES+403.54	2	>100	>100
85	4.6	ES+415.54	4	>100	>100
86	4.95	ES+ 399.59	3	>100	100
87	5.68	ES+439.51	4	50	50
88	5.64	ES+ 420,422	0.3	100	40
89	5.19	ES+ 431	0.8	>100	>100
90	5.11	ES+ 431	0.5	100	100
91	5.65	ES+ 420,422	0.3	100	100

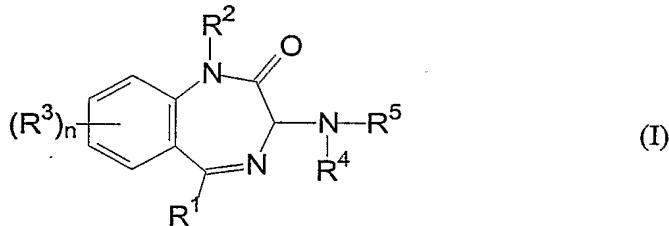
92	5.32	ES+ 404	<0.3	100	100
93	5.44	ES+431	<0.3	100	>100
94	4.91	ES+431	1.5	>100	>100
95	5.51	ES+431	1.5	100	>100
96	5.3	ES+ 414.54	5	>100	>100
97	5.14	ES+414.55	5	>100	>100
98	5.17	ES+ 414.54	5	>100	>100
99	5.69	ES+ 420.49	1	100	>100
100	5.58	ES+ 420.48	4	>100	100
101	5.36	ES+435.45	2.5	100	100
102	5.79	ES+ 435.46	7	>100	>100
103	5.69	ES+454.47	7	>100	30
104	5.69	ES+454.48	5	>100	>100
105	5.6	ES 454.49	9	>100	>100
106	5.7	ES+ 400	0.7	>100	>100
107	5.33	ES- 414	<0.3	60	60
108	5.32	ES+ 464, 466	2	>100	>100
109	509	ES+ 416.54	2	50	100
110	5.21	ES+ 431.53	5	>100	>100
111	5.29	ES+ 400.49	3	>100	>100
112	4.87	ES+ 468	1.5	>100	>100
113	4.69	ES+ 399	1.5	>100	>100
114	5.37	ES+ 386	5	>100	60
115	5.32	ES+ 399.50	1.5	>100	60
116	5.49	ES+455.45	2	20	20
117	5.67	ES+ 517.33, 519.33	6	60	100
118	5.14	ES+ 463.41, 465.41	2	>100	100
119	5.54	ES+ 439.40	2	>100	30
120	4.98	ES+ 399.55	6	>100	60
121	5.02	ES+ 416.49	4	60	60
122	5.2	ES+ 416.49	0.4	60	20
123	5.2	417.48	2	>100	100
124	5.02	ES439.41	5	70	60
125	5.84	ES+ 442.54	6.1		>50

126	4.61	ES+ 416.44	5.4		>50
127	4.35	ES+ 407.44	9.4		>50
128	4.65	ES+ 389.46	6.1		>50
129	4.53	ES+ 401.47	4.9		>50
130	4.95	ES- 437.35	9.7		39.5
131	4.82	ES+ 405.44	9.6		>50
132	5.39	ES+ 389	6.3		>50
133	4.26	ES+ 432	6.2		77.2
134	4.77	ES+ 414	6.5		77.1
135	5.2	ES+ 374.42	9.5		>50
136	5.07	ES+ 392.42	8.7		>50
137	5.65	ES+ 414.46	8.3		>50
138	5.25	482	8.3		51
139	4.99	ES+ 400	9.2		98
140	5.03	ES+ 435.45	2.5		68
141	4.82	ES+ 412.50	4.3		>50
142	4.78	ES+ 402.50	9.4		>50
143	4.3	ES- 463	3.8	>50	
144	4.54	ES+ 400	5.5	>50	
145	4.39	ES+ 400	1.9	>50	
146	5.08	ES- 401	9.5	>50	
147	5.02	ES+ 445	15.9	>50	
148	4.56	ES- 349.57	5	>100	>100
149	4.76	ES+ 377.57	1.5	>100	>100
150	3.87	ES+ 345.55	2	>100	>100
151	4.43	ES+ 351.58	1.5	>100	>100
152	5.17	ES+374	0.3	>100	100
153	5.01	ES+ 397.52	5	>100	>100
154	4.31	ES+ 328.49	3	>100	>100
155	4.95	ES+ 356.51	6	>100	>100
156	5.17	ES+ 380.46	1.5	100	100
157	5.51	ES+ 396.45	5	>100	100
158	5.74	ES+ 396.53	2	100	>100
159	5.15	ES+ 397.52	2	>100	>100

160	4.44	ES+ 391.48	10	>100	>100
161	5.52	ES+ 414	2	100	60
162	4.43	ES+ 358	2	>100	>100
163	4.67	ES+ 352.51	5	>100	>100
164	5	ES+ 392.56	4	100	100
165	5.14	ES+ 392.56	2	>100	>100
166	4.77	ES+ 393.57	5	>100	>100
167	4.42	387.52	9	>100	>100
168	5.43	ES+396.53	5	>100	>100
169	5.18	ES+ 376.44	5	50	30
170	4.42	ES+ 377.40	3.4		>50
171	4.43	ES+ 377.40	4.8		>50
172	4.61	ES+ 357	6.4		137.8
173	4.66	ES+ 346	8.3		95
174	4.06	ES+ 400.46	6.9		60
175	5.5	ES+ 450.50	8.2		>50
176	5.82	ES+ 458.46	4.3		99
177	5.17	ES+ 412.50	4.3		>50
178			4.3		>50
179	5.17	ES+ 504.20	3.9		>50
180	5.01	ES+ 396.46	2.6		37.1
181	4.23	ES+ 310.55	9.6		>50
182	4.47	ES+ 324.46	10		>50
183	4.89	ES+ 352.48	9.88		>50
184	5	390	9.5	>50	

CLAIMS

1. Use of a benzodiazepine derivative of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in treating or preventing an RSV infection



wherein:

- R¹ represents C₁₋₆ alkyl, aryl or heteroaryl;
- R² represents hydrogen or C₁₋₆ alkyl;
- each R³ is the same or different and represents halogen, hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, amino, mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, nitro, cyano, -CO₂R', -CONR'R'', -NH-CO-R', -S(O)R', -S(O)₂R', -NH-S(O)₂R', -S(O)NR'R'' or -S(O)₂NR'R'', wherein each R' and R'' is the same or different and represents hydrogen or C₁₋₆ alkyl;
- n is from 0 to 3;
- R⁴ represents hydrogen or C₁₋₆ alkyl;
- R⁵ represents C₁₋₆ alkyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C₁₋₆ alkyl)-, heteroaryl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆ alkyl)-, heterocyclyl-(C₁₋₆ alkyl)-, aryl-(C₁₋₆ hydroxyalkyl)-, heteroaryl-(C₁₋₆ hydroxyalkyl)-, carbocyclyl-(C₁₋₆ hydroxyalkyl)-, heterocyclyl-(C₁₋₆ hydroxyalkyl)-, aryl-C(O)-C(O)-, heteroaryl-C(O)-C(O)-, carbocyclyl-C(O)-C(O)-, heterocyclyl-C(O)-C(O)- or -XR⁶;
- X represents -CO-, -S(O)- or -S(O)₂-; and
- R⁶ represents C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C₁₋₆ alkyl)-, heteroaryl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆ alkyl)-, heterocyclyl-(C₁₋₆ alkyl)-, aryl-(C₁₋₆ alkyl)-

O-, heteroaryl-(C₁₋₆ alkyl)-O-, carbocyclyl-(C₁₋₆ alkyl)-O-, heterocyclyl-(C₁₋₆ alkyl)-O- or -NR'R'' wherein each R' and R'' is the same or different and represents hydrogen, C₁₋₆ alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C₁₋₆ alkyl)-, heteroaryl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆ alkyl)- or heterocyclyl-(C₁₋₆ alkyl)-.

5

2. Use according to claim 1 wherein:

- each R³ is the same or different and represents halogen, hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, amino, mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, nitro, cyano, -CO₂R', -CONR'R'', -NH-CO-R', -S(O)R', -S(O)₂R', -NH-S(O)₂R' or -S(O)NR'R'', wherein each R' and R'' is the same or different and represents hydrogen or C₁₋₆ alkyl;
- R⁵ represents C₁₋₆ alkyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C₁₋₆ alkyl)-, heteroaryl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆ alkyl)-, heterocyclyl-(C₁₋₆ alkyl)- or -XR⁶;
- X represents -CO-, -S(O)- or -S(O)₂-; and
- R⁶ represents C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C₁₋₆ alkyl)-, heteroaryl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆ alkyl)-, heterocyclyl-(C₁₋₆ alkyl)- or -NR'R'' wherein each R' and R'' is the same or different and represents hydrogen, C₁₋₆ alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C₁₋₆ alkyl)- or heteroaryl-(C₁₋₆ alkyl)-.

10

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3. Use according to either claim 1 or claim 2, wherein R¹ is C₁₋₂ alkyl or aryl.

4. Use according to any one of the preceding claims wherein R² is hydrogen.

5. Use according to any one of the preceding claims wherein R³ is halogen, hydroxy, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, amino, mono(C₁₋₄ alkyl)amino or di(C₁₋₄ alkyl)amino.

30

6. Use according to claim 5, wherein R³ is fluorine, chlorine, bromine, C₁₋₂ alkyl, C₁₋₂ alkoxy, C₁₋₂ alkylthio, C₁₋₂ haloalkyl, C₁₋₂ haloalkoxy, amino, mono(C₁₋₂ alkyl)amino or di (C₁₋₂ alkyl)amino.
- 5 7. Use according to any one of the preceding claims wherein R⁴ is hydrogen or C₁₋₂ alkyl.
8. Use according to any one of the preceding claims wherein R⁵ is C₁₋₆ alkyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C₁₋₄ alkyl)-, heteroaryl-(C₁₋₄ alkyl)-, carbocyclyl-(C₁₋₄ alkyl)-, heterocyclyl-(C₁₋₄ alkyl)-, aryl-C(O)-C(O)-, heteroaryl-C(O)-C(O)- or -XR⁶.
- 10 9. Use according to claim 8, wherein R⁵ is C₁₋₄ alkyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, phenyl-(C₁₋₂ alkyl)-, heteroaryl-(C₁₋₂ alkyl)-, phenyl-C(O)-C(O)-, heteroaryl-C(O)-C(O)- or -XR⁶.
- 15 10. Use according to claim 9, wherein R⁵ is C₁₋₄ alkyl, phenyl, thienyl, furanyl, isoxazolyl, pyridyl, cyclopentyl, cyclohexyl, benzothienyl, dihydrobenzofuranyl, phenyl-CH₂-, furanyl-CH₂-, phenyl-C(O)-C(O)-, thienyl-C(O)-C(O)- or -XR⁶.
- 20 11. Use according to any one of the preceding claims wherein X is -CO- or -S(O)₂-.
- 25 12. Use according to any one of the preceding claims wherein, when R⁶ is a group -NR'R'' wherein each R' and R'' is the same or different and represents hydrogen, C₁₋₄ alkyl, aryl, carbocyclyl, heterocyclyl, aryl-(C₁₋₄ alkyl)- or heteroaryl-(C₁₋₄ alkyl)-.
- 30 13. Use according to claim 12, wherein when R⁶ is a group -NR'R'' each R' and R'' is the same or different and represents hydrogen, C₁₋₄ alkyl, phenyl, thienyl, cyclohexyl, cyclopentyl or phenyl-CH₂-.

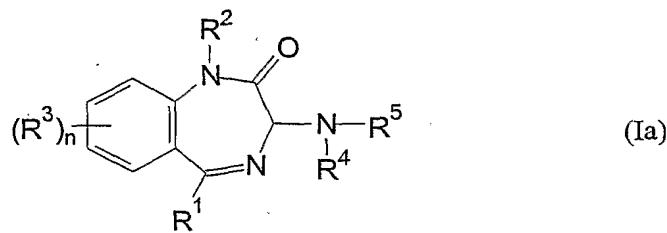
14. Use according to claim 13, wherein when R^6 is a group $-NR'R''$ and one of R' and R'' is hydrogen.

5 15. Use according to any one of the preceding claims wherein R^6 is C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-4} alkyl)-, heteroaryl-(C_{1-4} alkyl)-, carbocyclyl-(C_{1-4} alkyl)-, heterocyclyl-(C_{1-4} alkyl)-, aryl-(C_{1-4} hydroxyalkyl)-, heteroaryl-(C_{1-4} hydroxyalkyl)-, carbocyclyl-(C_{1-4} hydroxyalkyl)-, heterocyclyl-(C_{1-4} hydroxyalkyl)-, aryl-(C_{1-4} alkyl)-O-, heteroaryl-(C_{1-4} alkyl)-O-, carbocyclyl-(C_{1-4} alkyl)-O-, heterocyclyl-(C_{1-4} alkyl)-O- or $-NR'R''$.

10 16. Use according to claim 15, wherein R^6 is C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, phenyl-(C_{1-2} alkyl)-, phenyl-(C_{1-2} alkyl)-O-, heteroaryl-(C_{1-2} alkyl)-, phenyl-(C_{1-2} hydroxyalkyl)-, heteroaryl-(C_{1-2} hydroxyalkyl)- or $-NR'R''$.

15 17. Use according to claim 16, wherein R^6 is C_{1-4} alkyl, C_{1-4} alkoxy, phenyl, naphthyl, dihydrobenzofuranyl, benzodioxinyl, 9H-fluoren-9-onyl, indolyl, thienyl, furanyl, oxazolyl, isoxazolyl, pyrazolyl, pyridyl, benzothienyl, benzofuranyl, cyclopentyl, cyclohexyl, piperazinyl, piperidinyl, morpholinyl, phenyl-(C_{1-2} alkyl)-, phenyl- $CH_2-CH(OH)-$, phenyl- $CH(OH)-CH_2-$, phenyl-(C_{1-2} alkyl)-O-, 1H-benzo[*d*]imidazol-2(3*H*)-onyl or $-NR'R''$.

20 18. Use according to any one of the preceding claims wherein the benzodiazepine derivative of formula (I) is a benzodiazepine derivative of formula (Ia):



wherein:

- R^1 is phenyl or methyl;
- R^3 is methyl or chlorine;
- 5 - n is 0 or 1;
- R^4 is hydrogen or methyl;
- R^5 is phenyl- CH_2 -, furanyl- CH_2 -, thienyl-C(O)-C(O)- or - XR^6 ;
- X is -CO- or -S(O)₂-; and
- R^6 is C_{1-4} alkyl, C_{1-4} alkoxy, phenyl, naphthyl, dihydrobenzofuranyl, benzodioxinyl, 9H-fluoren-9-onyl, indolyl, thienyl, furanyl, oxazolyl, isoxazolyl, pyrazolyl, pyridyl, benzothienyl, benzofuranyl, cyclopentyl, cyclohexyl, piperazinyl, piperidinyl, morpholinyl, phenyl-(C_{1-2} alkyl)-, phenyl- CH_2 -CH(OH)-, phenyl-CH(OH)- CH_2 -, phenyl-(C_{1-2} alkyl)-O-, 1*H*-benzo[*d*]imidazol-2(3*H*)-onyl or - $NR'R''$ wherein each R' and R'' is the same or different and represents hydrogen, C_{1-4} alkyl, phenyl, thienyl, cyclohexyl, cyclopentyl or phenyl-(CH_2)-,

the phenyl moiety in the group R^1 being unsubstituted or substituted by a single fluorine, chlorine, C_{1-2} alkyl, C_{1-2} alkoxy, C_{1-2} alkylthio, C_{1-2} haloalkyl or C_{1-2} haloalkoxy substituent;

20 the aryl moieties in the groups R^5 and R^6 being unsubstituted or substituted by 1,2 or 3 substituents selected from fluorine, chlorine, bromine, iodine, C_{1-4} alkyl, C_{2-4} acyl, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, amino, mono(C_{1-4} alkyl)amino, di(C_{1-4} alkyl)amino, nitro, - CO_2R' , - $S(O)_2R'$ and - $S(O)_2NH_2$, wherein R' represents C_{1-2} alkyl;

25 the heteroaryl moieties in the groups R^5 and R^6 being unsubstituted or substituted by 1 or 2 substituents selected from fluorine, chlorine, bromine, C_{1-2} alkyl, C_{1-2} haloalkyl and di(C_{1-2} alkyl)amino; and

30 the heterocyclyl and carbocyclyl moieties in the R^6 group being unsubstituted or substituted by 1 or 2 substituents selected from fluorine, chlorine, bromine, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl and nitro.

19. Use according to any one of the preceding claims, wherein the medicament is for use in treating a patient who is a child under two years of age.
20. Use according to claim 19 wherein said child suffers from chronic lung disease.
21. Use according to any one of claims 1 to 18 wherein the medicament is for use in preventing RSV infection in an infant less than six years of age who was born after 32 weeks of gestation or less.
22. Use according to any one of the preceding claims, wherein the medicament is suitable for intranasal or intrabronchial administration.
23. Use according to any one of the preceding claims, wherein the medicament further comprises an anti-inflammatory compound or an anti-influenza compound.
24. Use according to claim 23 wherein the anti-inflammatory compound is budesonide or fluticasone.
25. Use according to claim 23 wherein the anti-inflammatory compound is a leukotriene antagonist, phosphodiesterase 4 inhibitor or TNF alpha inhibitor.
26. Use according to claim 23 wherein the anti-inflammatory compound is an interleukin 8 or interleukin 9 inhibitor.
27. Use according to any one of claims 1 to 22 wherein the medicament is coadministered with an anti-inflammatory compound, as defined in any one of claims 24 to 26, or an anti-influenza compound.
28. A method of treating a patient suffering from or susceptible to an RSV infection, which method comprises administering to said patient an effective

amount of a benzodiazepine derivative of formula (I), as defined in any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof.

29. A method according to claim 28, wherein said patient is a patient as defined
5 in any one of claims 19 to 21.

30. A method according to claim 28 or 329, wherein the benzodiazepine derivative or salt thereof is administered intranasally or intrabronchially.

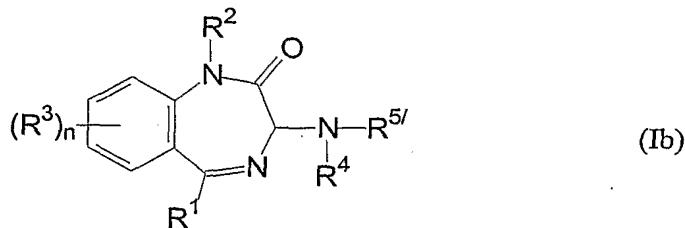
10 31. An inhaler or nebuliser containing a medicament which comprises
(a) a benzodiazepine derivative of formula (I), as defined in any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, and
(b) a pharmaceutically acceptable carrier or diluent.

15 32. A product comprising a compound of formula (I), or pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 18 and an anti-inflammatory compound, as defined in any one of claims 24 to 26, or an anti-influenza compound.

20 33. Use of a product according to claim 32 in the manufacture of a medicament for use in the treatment of concomitant RSV and influenza infections.

34. Use of a compound of formula (I), or pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 18 in the manufacture of a
25 medicament for use in the treatment of human metapneumovirus, measles, parainfluenza viruses, mumps, yellow fever virus (B5 strain), Dengue 2 virus or West Nile virus.

35. A benzodiazepine derivative of formula (Ib), or a pharmaceutically acceptable salt thereof
30



wherein:

- R¹ represents C₁₋₆ alkyl, aryl or heteroaryl;
- R² represents hydrogen, C₁₋₆ alkyl;
- each R³ is the same or different and represents halogen, hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, amino, mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, nitro, cyano, -CO₂R', -CONR'R'', -NH-CO-R', -S(O)R', -S(O)₂R', -NH-S(O)₂R', -S(O)NR'R'' or -S(O)₂NR'R'', wherein each R' and R'' is the same or different and represents hydrogen or C₁₋₆ alkyl;
- n is from 0 to 3;
- R⁴ represents hydrogen or C₁₋₆ alkyl;
- R⁵ represents C₃₋₆ alkyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C₁₋₆ alkyl)-, heteroaryl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆ alkyl)-, heterocyclyl-(C₁₋₆ alkyl)-, aryl-C(O)-C(O)-, heteroaryl-C(O)-C(O)-, carbocyclyl-C(O)-C(O)-, heterocyclyl-C(O)-C(O)- or -X', provided that when R⁵ is heteroaryl it is not 2-quinaldyl or 6-chloro-pyrazinyl, when R⁵ is heteroaryl-(C₁₋₆ alkyl)- it is not 2-indolylmethyl, 2-(3-indolyl)ethyl or 2-furanylmethyl, when R⁵ is aryl it is not unsubstituted phenyl and when R⁵ is aryl-(C₁₋₆ alkyl)- it is not unsubstituted phenyl-(C₁₋₂ alkyl)- or 4-chlorophenyl-(C₂₋₃ alkyl)-;
- X' represents -CO-R⁶', -S(O)-R⁶'' or -S(O)₂-R⁶'';
- R⁶' represents C₁ alkyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C₁₋₆ alkyl)-, heteroaryl-(C₁₋₆ alkyl)-, alkyl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆ alkyl)-, heterocyclyl-(C₁₋₆ alkyl)-, aryl-(C₁₋₆ alkyl)-O-, heteroaryl-(C₁₋₆ alkyl)-O-, carbocyclyl-(C₁₋₆ alkyl)-O-, heterocyclyl-(C₁₋₆ alkyl)-O- or -NR'R'' wherein each R' and R'' is the same or different and

represents hydrogen, C₁₋₆ alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C₁₋₆ alkyl)-, heteroaryl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆ alkyl)- or heterocyclyl-(C₁₋₆ alkyl)-, provided that (a) when R^{6/} is aryl it is not unsubstituted naphthyl, unsubstituted phenyl, mono-halophenyl, 5 4-methylphenyl, 4-methoxyphenyl, 4-hydroxyphenyl, 4-trifluoromethylphenyl, 4-nitrophenyl, 4-cyanophenyl, 4-n-propylphenyl, 4-t-butylphenyl, 4-n-pentylphenyl, 4-dimethylaminophenyl, 4-methylthiophenyl, 3-trifluoromethylthiophenyl, 3,4-dimethoxyphenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 2,3,4,5,6-pentafluorophenyl, 4-chloro-2-aminophenyl or 4-10 1,1-dimethylethylphenyl, (b) when R^{6/} is heteroaryl it is not 2-pyrrolyl, 2-pyrazinyl, 2-quinaldyl, 2-quinoxaliny, 1-methylindolyl, 2-methyl-indolyl, 2-benzofuranyl, 2-benzothienyl, 3-thienyl, 3-indolyl, unsubstituted 2-indolyl, 5-fluoroindol-2-yl, 5-chloroindol-2-yl, 5-bromoindol-2-yl, 5-hydroxyindol-2-yl or 5-methoxyindol-2-yl, (c) when R^{6/} is aryl-(C₁₋₆ alkyl)- it is not 4-15 thianaphthene-(CH₂)-, unsubstituted phenyl-(CH₂)-, 4-trifluoromethylphenyl-(CH₂)-, unsubstituted phenyl-(CH₂)₃-, monotrifluoromethylphenyl-(CH₂)₂-, 3-methoxyphenyl-(CH₂)₂-, 4-chloro-2-aminophenyl-(CH₂)₂-, 2,4-dichlorophenyl-(CH₂)₂-, monochlorophenyl-(CH₂)₂-, 2,4-trifluoromethylphenyl-(CH₂)₂-, 4-cyanophenyl-(CH₂)₂- or 3-cyanophenyl-(CH₂)₂-, (d) when 20 R^{6/} is heteroaryl-(C₁₋₆ alkyl)- it is not indolyl-(CH₂)_x-, wherein x is 1, 2, 3, unsubstituted furanyl-(CH₂)₂-, unsubstituted thienyl-(CH₂)₃- (e) when R^{6/} is carbocyclyl it is not cyclohexyl, (f) when R^{6/} is carbocyclyl-(C₁₋₆ alkyl)- it is not unsubstituted cyclohexyl-(CH₂)₁₋₃-, (g) when R^{6/} is heterocyclyl it is not N-pyrrolidinyl or 2-dihydrobenzofuranyl, (h) when R^{6/} is aryl-(C₁₋₆ alkyl)-O-25 it is not unsubstituted phenyl-(CH₂)-O-, and (i) when R[/] is hydrogen, R^{//} is not unsubstituted phenyl, 4-halophenyl, 3-halophenyl, methoxyphenyl, nitrophenyl, 2-chlorophenyl, 4-methylphenyl, dichlorophenyl, 3,5-dimethylphenyl, 3-methylphenyl, 3-cyanophenyl, 3-aminophenyl, 3-aminocarbonylphenyl, 3-benzoic acid, 3-benzoic acid ethyl ester, 6-amino-3-pyridyl, 5-(2-chloro)pyridyl, 5-(2-methoxy)pyridyl, 5-indanyl, unsubstituted 30 cyclohexyl, 1,1-dimethylethyl, unsubstituted phenyl-CH₂-, unsubstituted naphthyl or benzotriazol-3-yl and when R[/] is methyl, R^{//} is not

cyclopropylbenzene;

- $R^{6//}$ represents C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6} alkyl)-, carbocyclyl-(C_{1-6} alkyl)-, heterocyclyl-(C_{1-6} alkyl)-, aryl-(C_{1-6} alkyl)-

5 O-, heteroaryl-(C_{1-6} alkyl)-O-, carbocyclyl-(C_{1-6} alkyl)-O-, heterocyclyl-(C_{1-6} alkyl)-O- or - $NR'R^{6//}$ wherein each R' and $R^{6//}$ is the same or different and represents hydrogen, C_{1-6} alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6} alkyl)-, carbocyclyl-(C_{1-6} alkyl)- or heterocyclyl-(C_{1-6} alkyl)-; and

10 - $R^{6//}$ represents C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6} alkyl)-, carbocyclyl-(C_{1-6} alkyl)-, heterocyclyl-(C_{1-6} alkyl)-, aryl-(C_{1-6} alkyl)-O-, heteroaryl-(C_{1-6} alkyl)-O-, carbocyclyl-(C_{1-6} alkyl)-O-, heterocyclyl-(C_{1-6} alkyl)-O- or - $NR'R^{6//}$ wherein each R' and $R^{6//}$ is the same or different and represents hydrogen, C_{1-6} alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6} alkyl)-, carbocyclyl-(C_{1-6} alkyl)- or heterocyclyl-(C_{1-6} alkyl)-, provided that when $R^{6//}$ is aryl it is not 4-methylphenyl, provided that the compound of formula (Ib) is not N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-acetamide.

20

36. A benzodiazepine derivative according to claim 35 wherein:

- $R^{5/}$ is C_{3-6} alkyl, C_{3-6} cycloalkyl, heterocyclyl, C_{3-6} cycloalkyl-(C_{1-6} alkyl), aryl-C(O)-C(O)-, heteroaryl-C(O)-C(O)-, carbocyclyl-C(O)-C(O)-, heterocyclyl-C(O)-C(O)- or - X' ;

25 - X' is -CO- $R^{6/}$, -S(O)- $R^{6//}$ or -S(O)₂- $R^{6//}$;

- $R^{6/}$ is C_1 alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, heterocyclyl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6} alkyl)-O-, carbocyclyl-(C_{1-6} alkyl)-O-, heterocyclyl-(C_{1-6} alkyl)-O- or - $NR'R^{6//}$ wherein each R' and $R^{6//}$ is the same or different and represents hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, heterocyclyl, carbocyclyl-(C_{1-6} alkyl)- or heterocyclyl-(C_{1-6} alkyl)-;

30 - $R^{6//}$ represents C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6}

alkyl)-, carbocyclyl-(C₁₋₆ alkyl)-, heterocyclyl-(C₁₋₆ alkyl)-, aryl-(C₁₋₆ alkyl)-O-, heteroaryl-(C₁₋₆ alkyl)-O-, carbocyclyl-(C₁₋₆ alkyl)-O-, heterocyclyl-(C₁₋₆ alkyl)-O- or -NR'R'' wherein each R' and R'' is the same or different and represents hydrogen, C₁₋₃ alkyl, heterocyclyl, heteroaryl, heteroaryl-(C₁₋₆ alkyl)-, carbocyclyl-(C₁₋₆ alkyl)- or heterocyclyl-(C₁₋₆ alkyl)-; and

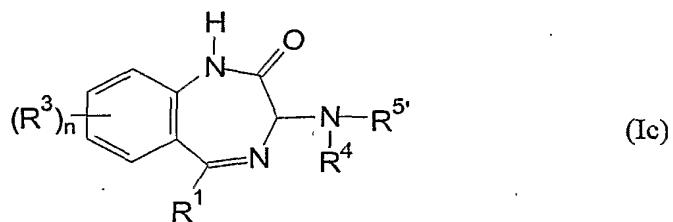
5 R^{6//} is C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₃₋₆ cycloalkyl, heterocyclyl, C₃₋₆ cycloalkyl-(C₁₋₆ alkyl)-, heterocyclyl-(C₁₋₆ alkyl)-, aryl-(C₁₋₆ alkyl)-O-, heteroaryl-(C₁₋₆ alkyl)-O-, carbocyclyl-(C₁₋₆ alkyl)-O-, heterocyclyl-(C₁₋₆ alkyl)-O- or -NR'R'' wherein each R' and R'' is the same or

10 different and represents hydrogen, C₁₋₆ alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C₁₋₆ alkyl)-, heteroaryl-(C₁₋₆ alkyl), carbocyclyl-(C₁₋₆ alkyl)- or heterocyclyl-(C₁₋₆ alkyl)-.

37. A benzodiazepine derivative according to claim 35 or claim 36 wherein R² is

15 hydrogen.

38. A benzodiazepine derivative of formula (Ic), or a pharmaceutically acceptable salt thereof,



wherein:

25

- R¹ is phenyl or methyl;
- R³ is methyl or chlorine;
- n is 0 or 1;
- R⁴ is hydrogen or methyl;
- R^{5'} is phenyl-CH₂- thienyl-C(O)-C(O)- or -X';
- X' is -CO-R^{6'}, -CONR'R'', -S(O)₂R^{6'''} or -S(O)₂-NR₂R₃; and

- R^{6i} is C_1 alkyl, C_{1-4} alkoxy, benzodioxinyl, 9H-fluoren-9-onyl, furanyl, oxazolyl, isoxazolyl, pyrazolyl, pyridyl, cyclopentyl, piperazinyl, piperidinyl, morpholinyl, phenyl- CH_2 - $CH(OH)$ -, phenyl- $CH(OH)$ - CH_2 -, phenyl-(C_2 alkyl)-O- or 1*H*-benzo[*d*]imidazol-2(3*H*)-only;
- 5 - $R^{6'''}$ is C_{1-4} alkyl, C_{1-4} alkoxy, phenyl, naphthyl, dihydrobenzofuranyl, benzodioxinyl, 9H-fluoren-9-onyl, indolyl, thienyl, furanyl, oxazolyl, isoxazolyl, pyrazolyl, pyridyl, benzothienyl, benzofuranyl, cyclopentyl, cyclohexyl, piperazinyl, piperidinyl, morpholinyl, phenyl-(C_{1-2} alkyl)-, phenyl- CH_2 - $CH(OH)$ -, phenyl- $CH(OH)$ - CH_2 -, phenyl-(C_{1-2} alkyl)-O- or 1*H*-benzo[*d*]imidazol-2(3*H*)-only;
- 10 - each R' and R'' is the same or different and represents hydrogen, C_{1-4} alkyl, phenyl, thienyl, cyclohexyl, cyclopentyl or phenyl-(CH_2)-; and
- each R_i and R_{ii} is the same or different and represents hydrogen, C_{1-4} alkyl, phenyl, thienyl, cyclohexyl, cyclopentyl or phenyl-(CH_2)-, wherein:
- 15 the phenyl moiety in the group R^1 being unsubstituted or substituted by a single fluorine, chlorine, C_{1-2} alkyl, C_{1-2} alkoxy, C_{1-2} alkylthio, C_{1-2} haloalkyl or C_{1-2} haloalkoxy substituent;
- 20 the aryl moieties in the groups R^{5i} , R^{6i} and $R^{6'''}$ being unsubstituted or substituted by 1,2 or 3 substituents selected from fluorine, chlorine, bromine, iodine, C_{1-4} alkyl, C_{2-4} acyl, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-6} haloalkyl, C_{1-4} haloalkoxy, amino, mono(C_{1-4} alkyl)amino, di(C_{1-4} alkyl)amino, nitro, - CO_2R' , - $S(O)_2R'$ and - $S(O)_2NH_2$, wherein R' represents C_{1-2} alkyl;
- 25 the heteroaryl moieties in the groups R^{5i} , R^{6i} and $R^{6'''}$ being unsubstituted or substituted by 1 or 2 substituents selected from fluorine, chlorine, bromine, C_{1-2} alkyl, C_{1-2} haloalkyl and di(C_{1-2} alkyl)amino;
- the heterocyclyl and carbocyclyl moieties in the $R^{6'''}$ group being unsubstituted or substituted by 1 or 2 substituents selected from fluorine, chlorine, bromine, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl and nitro;
- 30 the aryl, heteroaryl and carbocyclyl moieties in the R' and R'' being unsubstituted or substituted by one or two substituents selected from fluorine, chlorine, bromine, C_{1-2} alkyl, C_{1-2} alkoxy, C_{1-2} alkylthio, C_{1-2} haloalkyl and

nitro; and

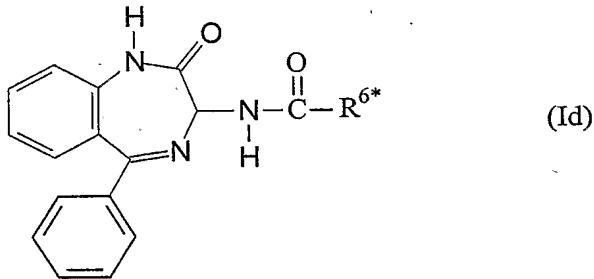
the aryl, heteroaryl and carbocyclyl moieties in the R₁ and R₂ being unsubstituted or substituted by one or two substituents selected from fluorine, chlorine, bromine, C₁₋₂ alkyl, C₁₋₂ alkoxy, C₁₋₂ alkylthio, C₁₋₂ haloalkyl and nitro,

5

provided that the compound of formula (Ic) is not N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-acetamide.

39. A benzodiazepine derivative of formula (Id), or pharmaceutically acceptable salts thereof

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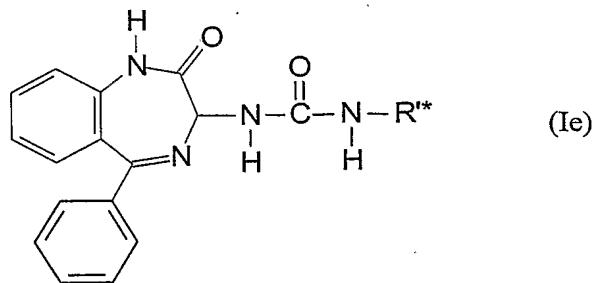


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wherein R^{6*} is an aryl group which is unsubstituted or substituted by 1, 2 or 3 substituents selected from halogen, C₁₋₆ alkyl, C₂₋₇ acyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, nitro, cyano, carbamoyl, mono(C₁₋₆ alkyl)carbamoyl, di(C₁₋₆ alkyl)carbamoyl, amino, mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, -CO₂R', -CONR'R'', -S(O)R', -S(O)₂R', -S(O)NR'R'', -S(O)₂NR'R'' -NH-S(O)₂R' or -NH-CO-R', wherein each R' and R'' is the same or different and represents hydrogen or C₁₋₆ alkyl, provided that R^{6*} is not a 4-chlorophenyl group.

20

40. A benzodiazepine derivative of formula (Ie) or a pharmaceutically acceptable salts thereof



wherein R^{1*} is an aryl group which is unsubstituted or substituted by 1 or 2 substituents selected from fluorine, chlorine, bromine, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy and nitro.

41. 1,1-Diethyl-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea
N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-propionamide
N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-butyramide
N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-isobutyramide
2,2-Dimethyl-N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-propionamide
Cyclopentanecarboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide
Cyclohexanecarboxylic acid 2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide
20. Piperidine-1-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide
Morpholine-4-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide
4-Methyl-piperazine-1-carboxylic acid -(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide
25. Benzo[b]thiophene-3-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

Isoxazole-5-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

Benzo[b]thiophene-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

5 N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-methanesulfonamide

Propane-1-sulfonic acid-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

Butane-1-sulfonic acid-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

10 N-(7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-isobutyramide

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-isonicotinamide

15 N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-nicotinamide

N-(7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-acetamide

(S)-2-Methoxy-4-nitro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

20 (S)-1-(2-Fluoro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea

2-Chloro-4-methanesulfonyl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

25 1-(4-Nitro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea

4-Methanesulfonyl-2-methoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

2-Methoxy-4-methylsulfanyl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

30 4-Methanesulfonyl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)terephthalamic acid methyl ester
5-Acetyl-2-ethoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide
5 3-Methoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-terephthalamic acid methyl ester
2-Methylsulfanyl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide
10 4-Amino-5-chloro-2-methoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide
4-Methanesulfonyl-2-methoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide
15 (S)-2,4,5-Trifluoro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide
(S)-5-Acetyl-2-ethoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide
2-Methoxy-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-5-sulfamoyl-benzamide
1-t-Butyl-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea
20 1-Cyclohexyl-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea
1-Ethyl-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea
1-Butyl-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea
25 4,5-Dimethyl-furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)amide
Piperidine-1-carboxylic acid (7-chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide
N-[5-(3-Chloro-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]acetamide
30 N-[5-(3-Chloro-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-isobutyramide

Cyclohexanecarboxylic acid [5-(3chloro-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-amide

Piperidine-1-carboxylic acid [5-(3-chloro-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-amide

5 N-[5-(3-Chloro-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]isonicotinamide

N-[5-(3-Methoxy-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-isobutyramide

Cyclohexanecarboxylic acid [5-(3-methoxy-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-amide

10 Piperidine-1-carboxylic acid [5-(3-methoxy-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-amide

Piperidine-4-carboxylic acid [5-(3-methoxy-phenyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-amide

15 Cyclohexanecarboxylic acid (8-chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

6-Morpholin-4-yl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-nicotinamide

Pyridine-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

20 6-Fluoro-4H-benzo[1,3]dioxine-8-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

1H-Pyrazole-4-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

25 6-Dimethylamino-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-nicotinamide

2-Ethoxy-naphthalene-1-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

9-Oxo-9H-fluorene-1-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

30 2-Oxo-2,3-dihydro-benzoimidazole-1-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)carbamic acid
tert-butyl ester

(S)-6-Fluoro-4H-benzo[1,3]dioxine-8-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

5 (S)-4,5-Dibromo-furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

(S)-3-Methoxy-naphthalene-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-carbamic acid
10 methyl ester

(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-carbamic acid
ethyl ester

(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-carbamic acid
isobutyl ester

15 2-Oxo-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-thiophene-2-yl-acetamide,
or a pharmaceutically acceptable salt thereof.

42. A benzodiazepine derivative according to any one of claims 35 to 41 for use
20 in a method of treating the human or animal body.

43. A pharmaceutical composition comprising a benzodiazepine derivative
according to any one of claims 35 to 41, or a pharmaceutically acceptable salt
thereof, and a pharmaceutically acceptable diluent or carrier.

25 44. A composition according to claim 43 comprising an optically active isomer of
a benzodiazepine derivative according to any one of claims 35 to 41.

45. A composition according to claim 43 or 44 which is in the form of a tablet,
30 troche, lozenge, aqueous or oily suspension, dispersible powders or granules.

INTERNATIONAL SEARCH REPORT

PCT/GB-03/04050

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D243/24 C07D409/12 C07D405/12 C07D413/12 C07D403/12
 C07D401/12 A61K31/5513 A61P31/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 14471 A (BALDWIN JOHN J; ELLIOTT JASON M (US); LIVERTON NIGEL (US); MERCK &) 1 June 1995 (1995-06-01) page 2, line 21 -page 6, line 33; examples 3,8,38,58; tables I,II,IV,V,VI page 33, line 22 - line 30 ---	35-40, 42-45
X	WO 93 17011 A (MERCK SHARP & DOHME) 2 September 1993 (1993-09-02) claims 1,6,7 ---	35,38, 40,42,43
X	WO 01 90084 A (GUIBLIN ALEXANDER RICHARD; MERCK SHARP & DOHME (GB); OWENS ANDREW) 29 November 2001 (2001-11-29) page 64, scheme 9, starting compound page 3, line 1 -page 20, line 7; claims 1-9 --- -/-	35,37, 42,43

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

3 February 2004

Date of mailing of the international search report

09/02/2004

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INTERNATIONAL SEARCH REPORT

PCT/GB03/04050

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 74783 A (DU PONT PHARM CO) 11 October 2001 (2001-10-11) claims 1,22; example 18 ---	35,42,43
X	WO 00 66106 A (UNIV MICHIGAN; GLICK GARY D (US); OPIPARI ANTHONY W JR (US)) 9 November 2000 (2000-11-09) claim 124 ---	35
A	WO 01 00611 A (JANSSENS FRANS EDUARD; SOMMEN FRANCOIS MARIA (BE); ANDRIES KOENRAA) 4 January 2001 (2001-01-04) abstract; claims 1,2,10-12 ---	1-34
A	EP 0 491 218 A (HOFFMANN LA ROCHE) 24 June 1992 (1992-06-24) claims 1,12,14,15 ---	1-45
A	WO 00 12547 A (DEPLA ERIK; INNOGENETICS NV (BE); MAERTENS GEERT (BE); MOEREELS HE) 9 March 2000 (2000-03-09) abstract page 4, line 13 -page 10, line 13 ---	1-45
A	WO 01 92235 A (DU PONT PHARM CO) 6 December 2001 (2001-12-06) page 164, formula 1b; page 165, formula 1c -----	35,37

INTERNATIONAL SEARCH REPORT

PCT/GB 03/04050

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 28-30 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/GB 03/04050

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